The New England
Journal of Medicine

Copyright, 1939, by the Massachusetts Medical Society

VOLUME 220 MAY 4, 1939 NUMBER 18

AN ANALYSIS OF THE TREATMENT AND MORTALITY OF THREE HUNDRED AND NINETY CASES OF ACUTE AGRANULOCYTIC ANGINA*

HENRY JACKSON, JR., M.D.,† AND THOMAS J. G. TIGHE, A.B.

BOSTON

THIS paper presents a critical analysis of the efficacy of various forms of treatment in 390 cases of acute agranulocytic angina reported in the literature since 1933. Papers confining themselves to summaries only and not giving actual case histories have not been included, for in such articles the data relative to both diagnosis and treatment are inadequate for proper study.

The evaluation of therapy by a survey of the literature is, of course, open to certain fundamental objections. It must, for instance, be remembered that therapeutic successes are more apt to be reported than are therapeutic failures, but this should be no truer for one type of treatment than for another, so that while the percentage of cures — under any form of treatment — is probably not so great as would appear from such a survey, it is improbable that any one group suffers more from this defect than does any other.

On the other hand, a survey of the existing literature has certain advantages in diseases such as that under consideration. It is impossible in the case of such an uncommon condition to have any one physician collect, in his own right, a series of sufficient magnitude to be of much statistical significance. Furthermore, from a statistical point of view, ten series of 10 cases each in the hands of so many different observers are probably more cogent than 100 cases under one man's control, for the personal element is largely eliminated. In any event, such a survey would seem, at present, the best available method of evaluating the various therapeutic agents so far advocated for this disease.

Leukopenia and neutropenia alone do not constitute the disease acute agranulocytic angina. The efficacy of any therapeutic agent in agranulocytic angina cannot be judged by its effect in other conditions associated with leukopenia and neutropenia, be they ever so marked.

True acute agranulocytic angina, also known as agranulocytosis, malignant granulopenia and acute primary granulocytopenia, may be defined as an acute disease characterized by extreme leukopenia and granulopenia. The red cells and platelets are essentially unaltered. There are very rarely any hemorrhagic manifestations. There are no, or at most extremely few, very immature white cells in the blood at the height of the disease. Neither liver nor spleen is noticeably enlarged, nor is there any lymphadenopathy other than that which may readily be explained by local sepsis. Death may occur within thirty-six hours of the apparent onset. Recovery, if it takes place, usually occurs within two weeks. Relapses occur, though they are uncommon. Rarely the disease is cyclic. While the etiology is still in some doubt, there is general agreement that many cases are caused by amidopyrine, dinitrophenol and similar compounds.[1] The bone marrow shows what appears to be a maturation arrest in the granular white-cell series at the stem-cell or myeloblast stage.[2, 3]

This disease must be sharply differentiated from leukemia with a low white-cell count, aplastic anemia, leukopenia due to overwhelming sepsis and chronic leukopenia due to various causes. This is not the appropriate place to discuss the differential diagnosis.[4, 5]

Of 448 cases reported as agranulocytic angina, 58 must be discarded because a scrutiny of the case reports fails to substantiate that diagnosis and indicates that the proper diagnosis was aplastic anemia, pernicious anemia, overwhelming sepsis, Hodgkin's disease, leukemia or some other funda-

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, the Department of Medicine, Harvard Medical School, and the Collis P. Huntington Memorial Hospital, Boston.

†Assistant professor of medicine, Harvard Medical School; associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

mental disorder associated with chronic leukopenia.

Seventy-five of the remaining 390 cases received no treatment aimed specifically at the bone-marrow dyscrasia. Death occurred in 78 per cent of these, a mortality rate essentially the same as that given by other authors.[6, 7] It may therefore be concluded, with some degree of assurance, that the mortality when no specific treatment is given is in the vicinity of 75 or 80 per cent.

In order to determine the value of a specific method of therapy, the agent must be given in adequate amounts and sufficient time must be allowed for it to act. If inadequate amounts are administered, or if adequate amounts have been given but the patient succumbs before beneficial action could result, the case must be considered as inadequately treated. The following types of cases must be placed in this class.

(1) Those in which the patients died before the treatment could have had time to influence the bone marrow to renewed activity, as evidenced by the rise of white cells in the peripheral blood. This time interval varies with the particular type of therapy used and will be discussed later.

(2) Those in which the patients recovered or showed unquestionable hematologic response to therapy in a similar time interval.

(3) Those in which the patients died without receiving adequate amounts of a given therapeutic agent, no matter how long they may have been hospitalized.

(4) Those in which the patients recovered under similar circumstances.

It would be expected that the mortality of these inadequately treated cases would be approximately the same as that of a series that had received no specific therapy whatever. This proves to be the case. Of the 130 cases, death occurred in 95, or 73 per cent.

The parenteral use of liver extract was first suggested by Foran, Sheaff and Trimmer.[8] They used a commercial preparation of the "fraction G" of Cohn, and injected the material derived from 100 gm. of liver into the vein or muscle every eight hours until a definite rise in the granulocytes or marked clinical improvement occurred. This dose has been accepted as the minimum requirement. Murphy[9] noted that "there was a prompt and often striking response in the number of white blood cells within a few hours of the beginning of treatment." Others have observed this phenomenon, but Witts, Willcox and Warner[10] point out that there is a definite fall in the leukocyte count in about eighteen hours, and conclude that liver produces a shock-like reaction suggesting peripheral mobilization of preformed cells rather than a stimulation of their production. It has also been claimed that the rise in white-cell count in pernicious anemia following parenteral liver therapy indicates a stimulating action on the leukocytes, but the relative leukopenia of pernicious anemia is essentially a myelophthisic one, and the slow rise of the white-cell count in this disease under liver therapy is due largely, if not entirely, to the maturation of the immature red cells and the consequent return of the bone marrow architecture to a normal state, thus permitting the unhampered multiplication of leukocytes.

The advocates of liver therapy have set no definite time for the appearance of a favorable response after treatment, but seventy-two hours has been taken as an arbitrary standard; any recovery before this time is regarded as spontaneous, and any death is attributed to inadequate therapy.

Nine cases have been reported in which adequate amounts of liver extract were the only specific therapy used. Eight other cases in which liver extract only was used must be eliminated because of inadequate treatment or because the data presented were insufficient for purposes of analysis. In the 9 adequately treated cases, 7 patients recovered and 2 died, a mortality of 18 per cent.

It would seem from the above figures that liver therapy was definitely successful in the treatment of agranulocytic angina. However, there are 17 other cases reported in the literature in which adequate amounts of liver extract were used together with some other specific method of treatment. If liver were as successful in its effect as the results of the first 9 cases suggest, a similar success would be expected in these 17 cases, since there is no reason to believe that any of the other measures used would interfere with any possible beneficial action of the liver. Yet 14 of the 17 patients died, giving a mortality of 82 per cent. Combining the two series of cases, the mortality of agranulocytic angina treated with liver is found to be 62 per cent.

From these figures, it may be concluded that the 7 recoveries in the 9 cases treated with liver extract alone were due to chance, and that the 62 per cent mortality of the combined series is a more just evaluation of the usefulness of liver extract in agranulocytic angina.

Stimulating doses of x-rays were first introduced as a therapeutic measure in agranulocytic angina by Friedemann and Elkeles,[11] and have been used by many others since that time. There has been much conflict of opinion as to whether large or small doses should be used. Therefore, any therapeutic exposure has been considered to be adequate.

Only 5 cases have been reported in the literature since 1933 that were treated by x-ray alone. Of

these, 4, or 80 per cent, were fatal. The number of cases is too small to be significant. However, 22 other cases have been reported that have received x-ray treatment as well as some other form of therapy. Of these patients 14 died, a mortality of 64 per cent. The mortality for cases treated by x-ray alone and x-ray combined with some other form of therapy is therefore 67 per cent. The figure obtained in a series of 27 cases is probably significant, and the mortality of 67 per cent in this series, shows that x-ray therapy is of little value in the treatment of agranulocytic angina.

Transfusion has been suggested by some as a useful form of treatment. Any amount or number of transfusions have been considered adequate, and the time interval has been arbitrarily taken as seventy-two hours. Seventeen cases have been reported as treated by transfusion alone. Fourteen patients died, a mortality of 82 per cent, which is about the same as that of the untreated cases. Fifty-six cases were treated by transfusions together with some other type of therapy. Twenty-nine of these patients, or 53 per cent, died. The combined figures show that the mortality is 60 per cent.

There would seem to be a large discrepancy between the 82 per cent mortality of those cases receiving transfusions only and the 53 per cent mortality of the cases treated with transfusion together with other forms of therapy. But of these latter 56 cases, 24 also received adequate amounts of Pentnucleotide (N.N.R.) and 16 recovered. As 33 per cent is approximately the mortality of cases adequately treated with Pentnucleotide only,[5] and as the mortality of cases treated with transfusion alone is 82 per cent, it may properly be assumed that the recoveries in these 24 cases were due largely to Pentnucleotide. Therefore, the corrected mortality for cases treated by transfusion should be 74 per cent. The results in the entire series of cases receiving transfusion with or without other forms of therapy exclusive of those treated with Pentnucleotide indicate that transfusions decrease the mortality only 4 per cent. Transfusion, therefore, does not appear to alter materially the number of blood leukocytes or to affect favorably the bone marrow, and cannot be considered a specific remedy for agranulocytic angina.

Giffin and Watkins[12] have suggested that yellow bone marrow might be of value in agranulocytic angina on the theory that it contains a factor that overcomes the maturation arrest of the leukocytes. They recommend 300 to 500 gm. of desiccated marrow taken by mouth. Marberg and Wiles[13, 14] have treated patients with extracted bone marrow and report that a reaction may be expected in twenty-four to forty-eight hours. These latter authors have treated 26 cases with this method, but report only 8 in enough detail to be considered from a statistical point of view. Four of these patients recovered when bone-marrow extract only was used, and 3 when the extract was used with some other form of therapy. In the remaining case, bone-marrow extract was given when the patient had obviously started to recover and after Pentnucleotide had been administered in full doses on each of the preceding four days. Three other cases have been reported that received adequate bone marrow along with other forms of therapy. Of these, 1 patient died. Thus the mortality of all cases treated with yellow bone-marrow extract is 10 per cent. Giffin and Watkins[15] have recently reported a series of 24 cases that received bone-marrow extract only. The results in the series were excellent, but unfortunately the cases were not presented in sufficient detail to be included in the present analysis.

It is impossible to draw any definite conclusions from such a small series, but the apparent success of this method of therapy should stimulate its further use and study. It is to be noted, however, that because of the frequent presence of necrotic lesions and edema in and about the mouth in cases of agranulocytic angina, swallowing is often difficult or even impossible; therefore, any method of therapy that depends on oral administration may be limited.

"Leukocytic cream" injections have been advocated by Strumia[16] as a means of specific therapy. The dose recommended by the author is the "cream" from 100 to 150 cc. of whole normal human blood, injected intramuscularly daily. According to Strumia, a favorable response should be expected in from one to three days. He reports 5 cases treated by this method alone with 100 per cent recovery. One case has been reported where the treatment failed. Six additional cases have been reported where leukocytic cream was used with some other means of therapy. Of these patients, only 1 died. There is thus a combined mortality of 17 per cent. From such a small series one cannot draw any valid conclusions, yet the success in these cases warrants further study of this method of treatment.

Adenine sulfate was first advocated as a substance that might be specific in agranulocytic angina by Reznikoff[17] in 1930. At that time the dose recommended was 0.5 gm., injected intravenously twice daily. In 1933, Reznikoff[18] reported the results of 15 cases and set the standards for this method of treatment. The dosage then recommended was 1 gm., given intramuscularly three times a day, and recovery was expected to start in twenty-four to forty-eight hours. In the 15

cases, only 5 patients lived longer than twenty-four hours and all survived. Eight cases must be classified as inadequately treated either because of dosage or the time element. One patient recovered after adequate amounts of adenine sulfate together with other supposedly specific therapeutic agents. One recovered with transfusion and inadequate amounts of adenine sulfate. One other case has been reported that was cured by using adenine sulfate alone. Three further cases are on record that received this drug along with other therapeutic agents. Two of these patients died. The mortality of all these 10 cases treated with adequate amounts of adenine sulfate with or without other presumably specific agents is therefore 20 per cent.

Although the series is small, the 20 per cent mortality indicates that adenine sulfate should be given a more extensive trial in the future. It should be noted that this drug is one of the essential degradation products of Pentnucleotide.

Pentnucleotide was first suggested as a form of therapy by Jackson et al.[19] in 1931. In 1924 one of us[20] showed that normal human blood contained appreciable quantities of nucleotide, and later Doan[21] demonstrated that intravenous injections of this substance raised the peripheral white-cell count in normal rabbits. Pentnucleotide may be given intramuscularly or intravenously. In agranulocytic angina, 10 cc. of Pentnucleotide is given intramuscularly four times a day until the white-cell count has definitely risen and young neutrophils have appeared. In favorable cases, this change usually occurs from the third to the sixth day after the initiation of treatment. Ten cubic centimeters is then given once or twice a day until the white-cell count has been normal for several days. If there has been no response at the end of ten days, further therapy with Pentnucleotide is probably useless.[5] All cases which terminated fatally within forty-eight hours or which showed signs of recovery within seventy-two hours were considered as inadequately treated, and 20 cc. a day was taken as the minimum dose simply because this smaller dose was originally recommended by Jackson. None of the cases previously reported by Jackson and Parker[5] are included in the present analysis.

Forty-one cases of agranulocytic angina have been reported since 1933 that have been treated by Pentnucleotide only. Of these patients 12, or 29 per cent, died. Forty-four patients have been reported treated with adequate amounts of Pentnucleotide as well as some other form of therapy. Of these 18, or 40 per cent, died. The total mortality of the two groups of 85 cases is 35 per cent.

The 35 per cent mortality for these 85 cases recorded in the literature is essentially the same as Jackson and Parker's[5] mortality rate of 33 per cent reported in 1935 from a series of 103 cases.

The question may be raised as to whether it is proper to compare the mortality of patients treated with some specific therapy for at least seventy-two hours with that of patients who have not received any specific therapy (untreated cases) and who in some cases have not lived long enough to receive the theoretical benefits of seventy-two hours of general hospital care. The mortality of those cases which did not receive specific therapy but which were hospitalized and given general care for more than three days has therefore been determined. Of the 43 patients in this group, 30, or 70 per cent, died. This figure is but slightly lower than that for the untreated cases. It would therefore appear that a notable reduction in the mortality rate by any presumably specific agent given over a period of seventy-two hours could properly be attributed to the therapy.

Mortality Rates Following Various Types of Treatment in 390 Cases of Acute Agranulocytic Angina.

TREATMENT	NO. OF CASES	PERCENTAGE MORTALITY
Untreated	75	78
Inadequately treated	130	73
Liver extract	26	62
Alone	9	18
With other therapy	17	82
X-ray	27	67
Alone	5	80
With other therapy	22	64
Transfusion	73	60
Alone	17	82
With other therapy	56	53
Alone and with other therapy, exclusive of Pentnucleotide	49	74
Bone marrow	10	10
Alone	4	0
With other therapy	6	17
Leukocytic cream	12	17
Alone	6	17
With other therapy	6	17
Adenine sulfate	10	20
Alone	6	0
With other therapy	4	50
Pentnucleotide	85	35
Alone	41	29
With other therapy	44	40

SUMMARY AND CONCLUSIONS

Three hundred and ninety cases recorded in the literature since 1933 as agranulocytic angina have been analyzed in order to evaluate so far as possible the efficacy of the various therapeutic agents advocated as specific or helpful.

The mortality in 75 untreated cases was found to be 78 per cent.

The mortality in 43 cases which received no specific therapy but which received more than three days of general hospital care was 70 per cent.

The mortality in the 130 cases receiving inadequate amounts of any supposedly specific therapy was 77 per cent.

Neither transfusions nor x-ray therapy seemed to alter the mortality rate.

Treatment by yellow bone-marrow extract, leukocytic cream or adenine sulfate has not been widely enough reported upon to permit any accurate conclusions as to their worth. Because of the low mortality in the cases so far reported, these measures deserve further trial.

The mortality in the 26 cases treated with adequate amounts of liver extract was 62 per cent.

The mortality in the 85 cases treated with Pentnucleotide was 35 per cent, a figure closely approximating that reported by Jackson and Parker[5] in 1935. None of the latter cases are included in the present analysis.

At present, it would appear that Pentnucleotide in doses of at least 40 cc. a day is the most promising form of specific therapy in this disease.

Only the references specifically referred to in the text are listed below. A complete bibliography will appear in the reprints.

REFERENCES

1. Fitz-Hugh, T., Jr.: Sensitivity reactions of blood and bone marrow to certain drugs. J. A. M. A. **111**:1643-1647, 1938.
2. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Myeloid cell hyperplasia of the bone marrow in agranulocytic angina. Am. J. M. Sc. **183**:104-110, 1932.
3. Darling, R. C.; Parker, F., Jr., and Jackson, H., Jr.: The pathological changes in the bone marrow in agranulocytosis. Am. J. Path. **12**:1-12, 1936.
4. Jackson, H., Jr.: The differential diagnosis of agranulocytic angina from acute leukemia. Am. J. M. Sc. **188**:604-608, 1934.
5. Jackson, H., Jr., and Parker, F., Jr.: Agranulocytosis: its etiology and treatment. New Eng. J. Med. **212**:137-148, 1935.
6. Brogsitter, A. M., and von Kress, H.: Über die "Agranulocytose"-Krankheit. Eine Kritik der Kasuistik und eigene klinische Beoabachtungen. Virchows Arch. f. path. Anat. **276**:768-819, 1930.
7. Uffenorde, H.: Ausgedehnte Nekrotisierungen des Verdauungsschlauches bei Agranulocytose nebst Bemerkungen über die ursächlichen Bedingungen dieser Erkrankung. Virchows Arch. f. path. Anat. **287**:555-565, 1932.
8. Foran, F. L.; Sheaff, H. M., and Trimmer, R. W.: Agranulocytic angina; treatment by use of parenteral and oral liver extract; preliminary report. J. A. M. A. **100**:1917, 1933.
9. Murphy, W. P.: Parenteral use of liver extract in pernicious anemia. J. A. M. A. **98**:1051-1060, 1932.
10. Witts, L. J.; Willcox, W., and Warner, E. C.: Discussion on agranulocytosis. Proc. Roy. Soc. Med. **29**:671-688, 1936.
11. Friedemann, U., and Elkeles, A.: Die Roentgenbehandlung der Agranulozytose. Deutsche med. Wchnschr. **56**:947-950, 1930.
12. Giffin, H. Z., and Watkins, C. H.: Treatment of secondary anemia. J. A. M. A. **95**:587-592, 1930.
13. Marberg, C. M., and Wiles, H. O.: Yellow bone marrow extracts in granulocytopenia; preliminary report. J. A. M. A. **109**:1965, 1937.
14. *Idem:* Granulocytopoietic fraction of yellow bone marrow. Arch. Int. Med. **61**:408-429, 1938.
15. Giffin, H. Z., and Watkins, C. H.: Administration of yellow bone marrow in agranulocytic angina. Minnesota Med. **21**:62, 1938.
16. Strumia, M. M.: Effect of leukocytic cream injections in the treatment of neutropenias. Am. J. M. Sc. **187**:527-544, 1934.
17. Reznikoff, P.: Nucleotide therapy in agranulocytosis. J. Clin. Investigation **9**:381-391, 1930.
18. *Idem:* The treatment of agranulocytosis with adenine sulphate. J. Clin. Investigation **12**:45-53, 1933.
19. Jackson, H., Jr.; Parker, F., Jr.; Rinehart, J. F., and Taylor, F. H. L.: Studies of diseases of lymphoid and myeloid tissues; treatment of malignant neutropenia with pentose nucleotides. J. A. M. A. **97**:1436-1440, 1931.
20. Jackson, H., Jr.: Studies in nuclein metabolism. II. Isolation of a nucleotide from human blood. J. Biol. Chem. **59**:529-534, 1924.
21. Doan, C. A.: The neutropenic state; its significance and therapeutic rationale. J. A. M. A. **99**:194-202, 1932.

A CONSTRUCTIVE PROGRAM OF MEDICAL CARE FOR THE LOW-INCOME GROUP*

CHANNING FROTHINGHAM, M.D.†

BOSTON

ANY program for the medical care of the low-income group does not apply to the care of the indigent which is generally conceded to belong to government, either local, state or federal. Unfortunately the dividing line between the indigent and low-income groups is an exceedingly difficult one to draw, and the fact that it is drawn at different levels in different communities adds to the confusion.

The evidence is conclusive that medical care must be expensive for certain illnesses if it is to be good. Some provision, therefore, must be made for individuals in the low-income group to meet this cost, because all groups in our population must receive good medical care. Without trying to define just what the limits of income are for this group, it is fair to say that a very large number, probably more than half of our population, fall within it. Governmental compulsory health insurance has been suggested by the politicians as the means to provide good medical care for this large low-income group. Although compulsory health insurance as developed in some instances, such as the system adopted by the Southern Pacific Railroad, results in satisfactory medical service, there are grave doubts in the minds of most of the members of the medical profession in regard to the quality of medical care under such a system when provided by the government. These doubts are based on the experiences in other countries where, although the people say they are satisfied with the care they receive under what amounts to compulsory health insurance, the evidence suggests that the type of medical service offered is far from ideal. Furthermore, the experience has been that under governmental compulsory insurance plans it has been difficult for the individual to remain the private patient of his family physician, and it is generally conceded that better medical service results if patients have one chief medical adviser or family physician who is familiar with the environment of the patient and who knows something of the patient's background. In addi-

*Presented in part at a New England Town Meeting on the Air (Subject: "What Can the Medical Profession Offer in Place of Compulsory Health Insurance?"), Boston, February 21, 1939.

†President, Massachusetts Medical Society.

tion to the possibility of deterioration in medical service under a governmental compulsory health insurance plan, it is evident that such a plan suddenly applied to this country would create a tremendous overhead expense which might well be avoided if the government only took over its share of the financial burden for the care of the low-income group as the need for it became evident along evolutionary lines.

Many physicians believe that a constructive program can be worked out on a community basis so that the individual in the low-income group in any community may remain the private patient of his own physician without undue financial burden. The size of the individual community in which such a plan may be developed will naturally vary with the density of the population, the topography of the country and the means of transportation. The object of the plan is to spread throughout the community the cost of the medical care for the few unfortunate ones who have the types of illness that are expensive. In some communities, part of this cost can be borne by private philanthropy, as is done at the present time. Although large fortunes seem to be diminishing throughout the country, the endowment already involved in medical care will undoubtedly persist, and the ability to raise money for community chests suggests that additional funds from private sources will continue to be donated for this purpose for some years to come. However, private philanthropy will not be able to carry the entire load, and other means must therefore be developed to pay for the medical care of the individuals in the low-income group who need it. Some type of insurance against the expense of illness or financial assistance from public funds raised by taxation seems to be the most logical way to make up any deficiency after the resources of private philanthropy are exhausted.

With the development of the following three-point program in each community the individuals in the low-income group should be able to receive the best of medical care at a cost within their means. The program consists in: (1) a community hospital; (2) a non-profit insurance plan for the payment of hospital bills; and (3) a non-profit insurance plan for the payment of physicians' bills or some type of group or contract practice.

COMMUNITY HOSPITALS

As most of the patients who have illness which is costly have to be hospitalized, each community should have a hospital available for all its citizens. In such a hospital there should be proper equipment for practically all diagnostic procedures and treatment. In this way the expense of elaborate equipment for diagnosis and treatment will be borne by the community as a whole and will be available to all the citizens. In order to make it available to all citizens such a hospital must be opened to all *properly qualified* physicians of the community for the care of their private patients. Not many years ago only charity patients went to hospitals, and in order to avoid confusion in the care of these patients, the professional staffs of hospitals were limited to certain physicians. The result has been that in some communities still there is a tendency to believe that the staff of a hospital should be limited; but even if this is necessary, I believe it should only apply to the care of the charity patients. If a hospital is supported by the community, it is only proper that any member of the community should be allowed to be treated in the hospital by his own physician, provided that the physician is properly qualified. On the other hand, the trustees of such a hospital have responsibility in regard to the work done therein, and definite rules should therefore be established which limit a physician to practice only that type of medicine or surgery for which he is qualified. These community hospitals may be wholly supported by private philanthropy, as mentioned above, or there may be need of aid from the taxes collected in the community. It is also possible that some communities, even with the aid of local taxes, may not be able to support a properly equipped hospital, in which case the community would have to appeal to the public funds of the state, and if the latter were not able to support a sufficient number of community hospitals to serve its population it would be necessary to appeal to the federal government for aid. If it were necessary to appeal to the federal government for funds for any community it would be much more economical for the government to respond to such appeals individually than for it to set up an elaborate bureau to provide funds in general for the support of community hospitals.

INSURANCE FOR HOSPITAL BILLS

The second point in the program consists in the development of voluntary non-profit insurance plans to provide for the payment of hospital bills. The average cost throughout the country for this type of insurance, which usually covers three weeks of hospitalization, is about ten dollars a year for semi-private accommodations, and now an even cheaper rate is being developed for ward service. Such plans have developed on a tremendous scale in recent years, and the evidence shows that no non-profit voluntary plan organized on sound actuarial lines has failed since this movement started. Unfortunately, along with these suc-

cessful insurance plans, others based on less sound actuarial lines have sprung up which have not always been successful, and which have threatened to bring this type of insurance into disrepute among careless thinkers. An example of the demand by the public for such plans is the growth of the Associated Hospital Service Corporation of Massachusetts, popularly known as the Blue Cross. This corporation started out to insure only groups of employed people. The first policy was sold in October, 1937, and it was hoped that by the end of a year there might be 20,000 subscribers. At the end of a year and six months there were over 160,000 subscribers! Already this type of insurance has been made available to more people than were originally planned for, and it is hoped that as time goes on this type of insurance will be available for all the people.

INSURANCE FOR PHYSICIANS' BILLS

The third point in the program consists in the development of various non-profit plans of an insurance or contract nature to pay the physician's bill, so that the individual may remain the private patient of his family physician and meet the expense of specialism when necessary. There are many such plans in operation throughout the country, but not as yet many of a voluntary non-profit variety; the latter is in part due to the difficulty in securing proper statistics upon which to base actuarial tables. Another serious difficulty in the development of such plans has been the conservatism on the part of the medical profession toward approving specific insurance plans presented by interested individuals, especially if these plans suggest group or contract practice. There seems to be a fear on the part of organized medicine that contracts will lead to deterioration in medical service. The unpleasantness in the District of Columbia, which has resulted in the federal government suing organized medicine, apparently originated in the hostility of organized medicine to a contract arrangement for the payment of doctors to care for a group of individuals. That some types of contract or group medicine may lead to poorer medical service must be admitted, but organized medicine must realize that, in some instances, medical care may actually be better on a contract basis. The medical officers in the United States Army and the United States Public Health Service are on a contract basis, and the work of these physicians needs no criticism. Many industrial firms take excellent care of their employees by employing physicians on a contract basis, and many American colleges have contract physicians who care for their students with results far superior to those of former times. The actual facts are that some work may be done better on a contract basis and that in other instances the stimulation of the fee system produces better results. There is room for both methods of paying for medical service in this large country of ours.

In a discussion of any insurance or contract plan for paying physicians' bills one almost always hears the question, Does this permit the free choice of physician? Just when and how this expression arose in discussion of economic problems in medicine it is hard to say, but it probably originated with the development of compulsory insurance acts, such as those which cover industrial and automobile accidents in this country or of governmental insurance plans in other countries. With the former the private insurance companies involved in this work often tried to have the patients cared for only by the company doctors. The medical profession quite properly objected to this and succeeded in making it possible for an individual treated under these compulsory forms of insurance to have the physician of his choice. The threat that "free choice of physician" is eliminated in voluntary insurance and voluntary contract plans for the payment of physicians' bills is frequently used by objectors to these plans, but I insist improperly so. For if an individual voluntarily joins a plan for medical service in which it is known who the physicians are, it would seem that the individual is choosing those physicians just as freely as he chooses his physicians when he goes to one of the large private clinics of this country, of which there are many. Therefore, the medical profession should not let this expression "free choice of physician" interfere with the development of plans for distributing the cost properly created by physicians' bills.

Just what the cost will be per individual for insurance against appropriate physicians' bills for this class of patients cannot yet be as accurately judged as the cost of insurance against hospital bills, but enough plans have been tried to make it evident that it can be obtained at a figure within the reach of the low-income group.

If this three-point program is developed, there will be available for all the people of the country properly equipped hospitals which will provide aids for diagnosis and treatment which are too expensive for individual physicians or groups of physicians to maintain. The expense of these hospitals will be borne by the community as a whole, with the funds collected as mentioned above. Some of the support of these hospitals will be provided by the charges to patients who enter the hospital, but these hospital charges for the individual will be paid by the non-profit in-

surance companies, so that this cost will not be a severe financial burden on any one individual. Finally the physicians' bills will be paid by some non-profit insurance company or provided for on a contract basis so the individual will not have to meet any unusually high cost. By this program, therefore, the individual in the low-income group can remain the private patient of his own physician for the great majority of illnesses. Let us hope that by the development of such programs the individuals in the low-income group will be satisfied with their medical care, so that complaints from this large percentage of the population will not stimulate the politicians into governmental action aimed toward the establishment of compulsory health insurance.

THE ASSAY OF CRYSTALLINE AND URINARY ANDROGENS*

With Special Reference to Their Measurement by a Colorimetric Method

HARRY B. FRIEDGOOD, M.D.,† AND HELEN L. WHIDDEN, M.A.

BOSTON

RECENT advances in the physiology and biochemistry of the secretions of endocrine glands have made it possible to begin a study of certain phases of the complex problem of hirsutism in women. The importance of discovering the etiologic factors responsible for this condition and the measures necessary for its alleviation can be judged only in terms of the disfiguring nature of the affliction, the serious emotional disturbances which it initiates and the clinical disorders with which it is commonly associated.

The most recent advances in the study of hirsutism and virilism are being made along biochemical lines. Because of the obvious association between the biologic activity of male sex hormones and the physical characteristics of hirsutism and virilism, attention has been directed in such patients to the extraction and quantitative determination of urinary and blood constituents possessing the biological action of male hormones. Before studies of this type were undertaken, it had been determined that androgens are excreted normally in the urine of both men and women.[1-3] The total androgenic activity of normal male urine was found to be somewhat higher than that of normal female urine, although in many cases there was no obvious quantitative distinction.[1-3] The chemical nature of the androgens in normal female urine is still unknown except for traces of dehydroisoandrosterone (Callow[4]). In the urine of normal men the biological activity was traced in part to androsterone and dehydroisoandrosterone, which are present in approximately equal amounts.[4-6] Epi-etiocholanediol, a biologically inactive androgenic substance,[7] has also been isolated from the urine of normal men. Since these do not account for the entire androgenic activity of normal male urine, there must be other androgens which still remain to be identified.

Chemical methods for the extraction of urinary androgens have been perfected to a more satisfactory degree than have those for the recovery of androgens circulating in the blood.[8] The former method, therefore, has been used almost exclusively in the expectation that the level of excretion in the urine of substances with male sex hormone activity might give some indication of the nature of the pathologic physiology of the endocrine glands in hirsutism and virilism. However, quantitative determination of the biological activity of substances excreted in the urine is at present an unreliable method for estimating hormonal activity in the body. Justification for the use of such urinary assays as an index of the physiologic activity of certain endocrine glands necessitates assumptions for the support of which there is no reliable evidence at present. One must assume, for instance, that the total biological activity of the urinary androgens is either equal to or quantitatively proportional to the biological activity of the tissue androgens. As a matter of fact, the androgens which have been identified in urine are not identical in chemical structure with those extracted from endocrine tissues, although they are similar to them. Adrenosterone[9] and testosterone[10] have been extracted only from endocrine tissues; the former from adrenal cortex, the latter from testis. Androsterone,[11] dehydroisoandrosterone[5] and epi-etiocholanediol,[7] on the other hand, have been recovered only from urine extracts. It is not known precisely how these two groups of androgens are related physiologically to each other. Even were this relation well established, the bioassay of urinary androgens, as employed at present, could at best give only a crude idea of the

*From the Department of Medicine, Harvard Medical School, and the Medical Service of the Peter Bent Brigham Hospital.

A preliminary report presented before the Harvard Medical Society, November 22, 1938. Aided by grants from the Proctor Fund (1937-38) and the Milton Fund (1938-39).

†Instructor in medicine and research fellow in physiology, Harvard Medical School; junior associate in medicine, Peter Bent Brigham Hospital.

physiology of the male sex hormones, because such assays reveal merely the *total* biologic activity of a mixture of androgenic substances. The composition of this mixture is only partially known, only three of the androgens having been identified chemically in the urine of men, and no two of them possessing the same order of activity.[7, 12] The relative proportions in which urinary androgens are excreted are thus escaping attention and may have an important bearing on the normal and pathologic physiology of the tissue androgens.

The problem is complicated still further by the fact that less than 5 per cent of androgens administered by injection can be detected in the urine by bioassay.[4, 13, 14] Is this due to the method of their extraction which as yet is not fully developed, or is the hormone so altered during its activity in the body and its preparation for excretion that it becomes unrecognizable even as a degradation product in the urine? It is known, of course, that sex hormones may be secreted in one form (for example progesterone) and excreted in another (sodium pregnanediol glycuronidate).[15] This possibility must be taken into consideration, therefore, in connection with the apparent discrepancy between the intake and output of androgenic substances.

As might be expected from this survey of the problem, the results of urinary bioassays in hirsutism and virilism have added but little to our understanding of these conditions except in those patients whose virilism is due to an adrenocortical tumor. The total urinary androgens in hirsutism or virilism (not due to adrenal tumors) are either within normal limits or only moderately elevated.[4, 16, 17] The total urinary androgens in patients with virilism due to adrenocortical tumors, however, are unusually high and, therefore, of distinct diagnostic importance.[4, 18] In 1 such case Callow traced 70 per cent of this androgenic activity to dehydroisoandrosterone.[19] In cases of adrenal hyperplasia, Butler and Marrian isolated isoandrosterone and pregnane-3,17,20-triol from the urine.[20, 21] This may be significant because these androgens have not been found in the urine of normal people. In spite of the difficulties which have been pointed out, it is studies such as these, in addition to those of normal people which necessarily preceded them, which have given us a point of departure from which to extend further investigations more advantageously.

Aside from the fact that at present one cannot make use of the urinary androgens as an index to the biological activity of the tissue hormones, the usefulness of this method is impaired still further by other considerations. The results obtained by bioassay, as it is now being practiced, are dependent in large measure on variables which significantly affect their quantitative accuracy and which at present are not strictly controllable. In support of this contention one may cite the following:

(1) The capon method of bioassay has no sharply defined end point, because a capon unit is ordinarily defined in terms of an average increase in comb growth in a limited number of caponized birds. Because of inherent biological differences, particularly in capons not belonging to a highly inbred strain, the dosage-response relation varies considerably in individual animals. As the number of animals used in a test is limited, only three to five birds being employed for most assays, there is a distinct possibility of introducing significant errors in such determinations. Recognizing this difficulty, Koch[12] advocates the use of more capons per test.

(2) The results of capon assays vary considerably even if the technic is fundamentally the same. In the hands of various investigators the capon unit has been assigned values ranging from 100 to 200γ crystalline androsterone.[22–26] Moreover, if the method of hormone administration is changed from intramuscular injections to the application of androgens directly to the capon's comb by inunction, the biological effect of the androgen may be enhanced by more than fifty times.[27–30]

(3) Furthermore, the order of activity of various androgens likewise depends on their method of administration. With the intramuscular technic testosterone is six times as active and dehydroisoandrosterone one third as active as androsterone,[12] but testosterone and androsterone are similar in activity when given by inunction.[28]

(4) The nature of the solvent in which the hormone is administered may alter radically the biological effect of a given androgen. In the comb-growth method and in the castrate-rat assay the use of alcohol as a solvent for androsterone enhances its activity twofold as compared with oil.[26, 31]

(5) Finally, if the castrated rat is used for bioassay, the presence of certain substances, some of which are unknown, greatly increases the androgenic activity of hormones or hormone-like chemical substances. David and Freud and their collaborators[32, 33] have isolated from the testis what they have termed an *X* substance which greatly activates androgens such as testosterone, when the latter is tested on the accessory sex organs of the castrated rat. It has been demonstrated also that certain of the higher fatty acids, notably palmitic acid, possess this property of activating androgens.[34]

One may conclude from this brief critique that the bioassay of the *total* androgen content of urine has only a limited usefulness in clinical medicine. So far as is now known, the total urinary androgen is elevated significantly only in cases of virilism due to adrenal tumor. The results of bioassay may be more significant when all the urinary androgens are isolated and identified, and the nature of their physiologic and biochemical relation to the tissue androgens is established. No one knows as yet whether the relative proportions in which various urinary androgens are excreted are significant in health and disease. For clinical purposes, there-

fore, it is advisable to substitute for the bioassay a less laborious and less expensive technic, which necessitates no greater assumptions than are already being made with the method of bioassay. Such a technic became possible following the establishment of the chemical structure of certain of the androgens and closely related steroids. This method of assay is based on a colorimetric reaction, which was applied to the quantitative estimation of crystalline and urinary androgens. We have proved to our own satisfaction that by means of it one may assay quantitatively crystalline androsterone and dehydroisoandrosterone, and that it is adaptable to the assay of urinary androgens.

The colorimetric method of assaying androgens was first described by Zimmermann.[35, 36] It was modified later by Wu and Chou,[37] Oesting,[38, 39] and Callow, Callow and Emmens.[40] This method of assay is based essentially upon a nonspecific chemical reaction in which substances containing a $-CH_2 \cdot CO$ group react in an alkaline alcoholic solution with metadinitrobenzene to produce characteristic colors. The shade and intensity of these colors depend on a number of variables, such as the temperature of the reaction, the duration of the reaction, the concentration and amount of the alkali, the concentration and amount of the metadinitrobenzene, the relative proportions of alcohol and water, and illumination.

Although Oesting[38,39] develops his colors at room temperature, we have found, as have all other investigators,[36, 37, 40] that it is necessary to control all these factors rigidly. By modifying certain of the aforementioned variables, we increased the sensitivity of the reaction tenfold as compared with Oesting's modification, and succeeded in eliminating the development of interfering browns which affect the accuracy of the colorimetric determinations.

The procedure for color development according to our modification of the Zimmermann reaction for use in the Oesting colorimeter was applied to the assay of crystalline androsterone and dehydroisoandrosterone in the following manner:

Aliquot portions of an alcoholic hormone solution of known concentration are measured accurately into Oesting's colorimeter tubes, using a previously calibrated 1-cc. pipette graduated in 0.01 cc. The alcohol is evaporated off carefully over a water bath at 70–75°C., and after cooling the tubes to room temperature, 0.15 cc. of 95 per cent ethyl alcohol, 0.2 cc. of 2 per cent metadinitrobenzene in absolute ethyl alcohol and 0.2 cc. of 15 per cent aqueous potassium hydroxide are added to each tube. Their contents are then mixed thoroughly. At the same time a control tube containing identical amounts of the two reagents and alcohol is prepared. The tubes are placed in the dark in a water bath maintained at precisely 25°C. and, with occasional shaking, are kept there for one and a quarter hours. The contents of the tubes are then diluted to a volume of 7 cc. with 95 per cent ethyl alcohol. After being thoroughly mixed, they are assayed immediately in the Oesting colorimeter, which is set up with the necessary precautions to ensure optimal lighting conditions.

Using our modification of the Zimmermann reaction, we first calibrated Oesting's colorimeter with known quantities of crystalline androsterone and dehydroisoandrosterone. Oesting failed to take this precaution and relied wholly on capon assays of urinary androgens (unknowns) for the development of the color and the standardization of the disks in his colorimeter.[38, 39] As a result of our studies we reached the following conclusions:

(1) The intensity of the pink-to-red color which develops is proportional to the amount of hormone present in solution.

(2) The disks of the Oesting colorimeter representing color units below 2.0 are unreliable for quantitative assays.

(3) When colors are developed by Oesting's method and assayed with his colorimeter, 1 color unit is equivalent to approximately 100γ crystalline androsterone, whereas originally he claimed that a color unit was equivalent to $10 \pm 2\gamma$ androsterone. According to our method 1 color unit is equivalent to 8.96 to 10.04γ crystalline androsterone, depending on the disk used for a given determination. Calibration of the instrument with crystalline androsterone has resulted in the following values for each of the disks:

DISK MARKING	AVERAGE AMOUNT ANDROSTERONE PER UNIT	ANDROSTERONE EQUIVALENT OF EACH DISK
2.0 units	8.96γ	17.92γ
2.8 units	9.04γ	25.31γ
3.4 units	9.84γ	33.46γ
4.0 units	10.04γ	40.16γ
5.0 units	9.63γ	48.15γ

(4) Crystalline dehydroisoandrosterone gives a more intense pink color per unit of weight than does crystalline androsterone. Quantitatively, it is less of a complicating factor than already exists in the marked differences which are characteristic of the biological activity of these hormones. Further data on this point are being reported in another communication.

Having calibrated each colored disk of Oesting's colorimeter in terms of γ-equivalent crystalline androsterone, we then applied our modification of Zimmermann's reaction to the assay of urinary androgens in normal and hirsute women in order to determine whether one could for purely clinical purposes substitute the chemical method for that of bioassay.

Extraction and purification of the androgenic substances were done by a modification of the method of Gallagher et al.[17] This process effectively separates androgens from substances such

as acetoacetic acid, creatinine, estrogens and other phenols which might have a ketonic group, and which would therefore interfere with the accuracy of the results obtained by the chemical procedure.

Our patients were studied for from two to eight weeks; their urines were collected in twenty-four amounts three times a week and prepared for assay within twenty-four to forty-eight hours after collection. We have reported the results of assays in color units read directly from the instrument and have stated their equivalents in crystalline androsterone. The amount of the ketonic sterols in the neutral fraction of the urinary extracts can be estimated, therefore, in terms of crystalline androsterone. In this way the results of chemical assay are made comparable with those obtained by bioassay.

Although the detailed results of our clinical studies are being reported elsewhere, we wish to indicate here to what extent our chemical method of assay has been applied to the practical problems of clinical endocrinology. Extensive observations have been made on 3 normal women, 21 individuals with hirsutism and 2 patients with virilism due to adrenocortical tumors. The urines of the normal women were assayed three times a week for four weeks; those of the patients with hirsutism three times a week for four to eight weeks. The patients with adrenal tumors were studied at similar intervals for one month and twelve months, respectively. Normal young women excreted the equivalent of 4 to 15 mg. of androsterone per twenty-four hours. As the series grows larger, we expect that the lower limit will decrease, the upper limit probably will not change appreciably. Patients with hirsutism excreted the equivalent of 1 to 29 mg. of androsterone per twenty-four hours. Most of the results in this group fell within the normal range; relatively few excreted the equivalent of over 20 mg. of androsterone per twenty-four hours. There seemed to be no fixed relation between the extent of hirsutism and the total androgen excretion. Mild cases of hirsutism do not ordinarily excrete large amounts of androgen, and extensive cases also may excrete relatively small quantities. The most remarkable excretion of androgens is encountered in patients with virilism resulting from adrenocortical tumors. In 2 such cases[41] we found the androgen excretion to be the equivalent of 45 and 325 mg. of androsterone per twenty-four hours at various stages of the disease. The highest values appeared when the malignancy metastasized.

Callow, Callow and Emmens[40] have demonstrated that there is a statistically significant correlation between the results of bioassay and those derived from the chemical test. Although Callow and her colleagues have employed a modification of Zimmermann's reaction which differs from ours, the results from both laboratories are essentially the same.[40] In their series normal women excreted <2.2 to 9.9 mg. sterone per day; hirsute patients excreted <2.2 to 33 mg. and patients with adrenal tumors excreted 150 to 175 mg. Their phrase "milligrams sterone" refers to the amount of color-producing ketonic substances in the urine and represents the chromogenic equivalent of crystalline androsterone.

Callow's studies and ours are also in substantial agreement on other points in the colorimetric assay of urinary androgens:

(1) As measured colorimetrically, the androgen excretion of normal and hirsute patients may vary considerably from day to day just as has been reported for the bioassay.

(2) The colorimetric determination of urinary androgens yields higher values than can be obtained by bioassay. This is not at all surprising, for several reasons. In the first place, urine probably contains biologically inactive ketonic sterols, which are chemically closely related to androsterone and dehydroisoandrosterone and behave similarly from a chemical viewpoint. In the second place, there may be non-androgenic substances in the urine, as yet unknown, which react like androsterone with metadinitrobenzene. If present at all, they are there in only relatively small quantities, judging from the results obtained from bioassay and colorimetric assay.

DISCUSSION

The chemical (colorimetric) method gives consistent results, and there is a significant correlation between these results and those obtained by bioassay. Because it incurs less expense and is less time-consuming the chemical method is probably superior for clinical use to that of bioassay. It is apparent from our own data and that of Callow's that the chemical method can be used more advantageously in the diagnosis of adrenocortical tumors in patients with virilism. We are in agreement with reports in the literature that there is an excessive daily excretion of androgen in cases where an adrenocortical tumor exists, and Callow has found that 70 per cent of this androgenic activity can be accounted for by dehydroisoandrosterone. The remarkably high values for urinary androgens thus far seem to constitute an important differential point between the benign type of hirsutism and that caused by a neoplasm. It remains for further investigation to determine whether these strikingly elevated values for the urinary androgens are specifically characteristic

of the virilism associated with adrenocortical tumors. We have not yet had the opportunity of making such studies in arrhenoblastoma of the ovary, and thus far neither we nor others have found values of this order in Cushing's syndrome without an adrenocortical tumor.

We have demonstrated, furthermore, that the colorimetric assay of urinary androgens may yield information of prognostic importance, because by means of it we were able to predict the postoperative recurrence of an adrenal tumor about four months before clinical evidence of metastasis was first apparent.[41]

It is also evident that little further can be gained in the investigation of the pathologic physiology of hirsutism and virilism by studying only the total daily androgen excretion. More rapid progress assuredly will be made after it becomes possible to isolate quantitatively and to identify chemically the various urinary androgens. Such investigations may disclose qualitative differences between the androgens of normal and hirsute women. Butler and Marrian[20, 21] have already isolated isoandrosterone and pregnane–3,17,20–triol from the urine of patients with virilism and adrenal hyperplasia; these androgens have not been found in the urine of normal women.

Kenyon et al.,[17] Gallagher et al.,[3] Glass and Bergman[42] and others, who have investigated the androgen-estrogen ratio in normal women and in those with hormonal disturbances, have reported interesting findings on this aspect of the problem. It is quite possible that a relative increase in androgen production, and consequently in excretion, may account for certain types of hypertrichosis. This seems a likely explanation for the hirsutism in one of our patients who developed hypertrichosis during a six-month period of amenorrhea which began at the time of a severe streptococcal infection. With the reappearance of the menses the growth of new hair stopped, but the hair already present remained unchanged.

SUMMARY

The quantitative determination of urinary androgens by bioassay has various limitations which curtail its usefulness in the study of the pathologic physiology of hirsutism and virilism and in its practical application to the problems of clinical medicine. For these and other reasons it is proposed to supplant the method of bioassay, for purely clinical purposes, by a chemical technic which necessitates no greater assumptions than are already being made by those who use the bioassay exclusively.

The chemical method of assay is based on a colorimetric reaction (Zimmermann's) by means of which one may, with significant accuracy, quantitatively assay the crystalline androgens. This method also has been adapted satisfactorily to the assay of urinary androgens.

Oesting's colorimeter has been calibrated in terms of crystalline androsterone, and its limits of accuracy defined. It has been determined that Oesting's modification of Zimmermann's reaction is not adequately sensitive for quantitatively accurate assays. Our own modification of the Zimmermann reaction is about ten times as sensitive as that of Oesting.

The chemical method of assaying urinary androgens gives information of diagnostic and prognostic importance in certain cases of virilism. Preliminary studies have indicated that the androgen excretion for normal young women is the equivalent of 4 to 15 mg. androsterone per twenty-four hours, and that patients with benign hirsutism and adrenogenital virilism excrete the equivalent of 1 to 29 mg. androsterone per twenty-four hours. In 2 cases of virilism due to adrenocortical tumor the androgen excretion was found to be the equivalent of 45 and 325 mg. androsterone per twenty-four hours at various stages of the disease. In 1 of these cases[41] the androgen excretion fell to normal levels immediately after the removal of the tumor, but began to increase again about four months before clinical evidence of recurrence was detected.

Assay of the total urinary androgen excretion, either by the chemical or the biological method, can give only a crude index to the physiology of the male sex hormones until it becomes possible to identify chemically and to assay quantitatively each of the urinary androgens and to establish the physiological relation of the glandular hormones to those excreted in the urine.

370 Commonwealth Avenue.

REFERENCES

1. Womack, E. B., and Koch, F. C.: The testicular hormone content of human urine. Endocrinology **16**:273-277, 1932.
2. Dingemanse, E.; Borchardt, H., and Laqueur, E.: Capon comb growth-promoting substances ("male hormones") in human urine of males and females of varying ages. Biochem. J. **31**:500-507, 1937.
3. Gallagher, T. F.; Peterson, D. H.; Dorfman, R. I.; Kenyon, A. T., and Koch, F. C.: The daily urinary excretion of estrogenic and androgenic substances by normal men and women. J. Clin. Investigation **16**:695-703, 1937.
4. Callow, R. K.: Significance of excretion of sex hormones in urine. Proc. Roy. Soc. Med. **31**:841-856, 1938.
5. Butenandt, A.; Dannenbaum, H.; Hanisch, G., and Kudszus, H.: Über Dehydroandrosteron. Ztschr. f. physiol. Chem. **237**:57-74, 1935.
6. Dingemanse, E., and Laqueur, E.: Estimation of (capon) comb growth hormone in urine. Biochem. J. **32**:651-655, 1938.
7. Butenandt, A.; Tscherning, K., and Dannenberg, H.: Über epi-Ätiocholandiol-3,17 aus Männerharn. Ztschr. f. physiol. Chem. **248**:205-212, 1937.
8. McCullagh, D. R., and Osborn, W. O.: Male sex hormones of human urine and blood. J. Biol. Chem. **126**:299-303, 1938.
9. Reichstein, T.: Andrenosteron. Über die Bestandteile der Nebenniere-urinde II. Helvet. chim. acta **19**:223-225, 1936.
10. Laqueur, E.; David, K.; Dingemanse, E., and Freud, J.: Über männliches Hormon. Unterschied von Androsteron aus Harn und Testosteron aus Testes. Acta brev. Neerland. **5**:84, 1935.
11. Butenandt, A.: Über die chemische Untersuchung der Sexualhormon. Ztschr. f. angew. Chem. **44**:905, 1931.
12. Koch, F. C.: Male sex hormones. Physiol. Rev. **17**:153-238, 1937.

13. Kochakian, C. D.: Excretion of male hormones. Endocrinology **21**:60-66, 1937.
14. Dorfman, R. I.: The excretion of androgenic substances after the administration of testosterone. J. Biol. Chem. **123**:30, 1938.
15. Venning, E. H., and Browne, J. S. L.: Studies on corpus luteum function; urinary excretion of sodium pregnanediol. Endocrinology **21**:711-721, 1937.
16. Simpson, S. L.; de Fremery, P., and Macbeth, A.: The presence of an excess of "male" (comb-growth and prostate-stimulating) hormone in virilism and pseudo-hermaphroditism. Endocrinology **20**:363-372, 1936.
17. Kenyon, A. T.; Gallagher, T. F.; Peterson, D. H.; Dorfman, R. I., and Koch, F. C.: The urinary excretion of androgenic and estrogenic substances in certain endocrine states: studies in hypogonadism, gynecomastia and virilism. J. Clin. Investigation **16**:705-717, 1937.
18. Slot, W. J. B.: The relation of sex hormones in a case of virilism by hypernephroma. Acta med. Scandinav. **89**:371-375, 1936.
19. Callow, R. K.: Isolation of the male hormone present in the urine of a patient with an adrenal tumor. J. Soc. Chem. Ind. **55**:1030, 1936.
20. Butler, G. C., and Marrian, G. F.: Isolation of pregnane-3,17,20-triol from urine of women showing adreno-genital syndrome. J. Biol. Chem. **119**:565-572, 1937.
21. *Idem:* Chemical studies on adreno-genital syndrome; the isolation of 3(α)-hydroxyetiocholane-17-one,3(β)-hydroxyetioallocholane-17-one (isoandrosterone), and new triol from urine of a woman with an adrenal tumor. J. Biol. Chem. **124**:237-247, 1938.
22. Gallagher, T. F., and Koch, F. C.: Quantitative assay for testicular hormone by comb-growth reaction. J. Pharmacol. & Exper. Therap. **55**:97-117, 1935.
23. Freud, J.; de Fremery, P., and Laqueur, E.: Eichung des "männlichen" Hormons mit Hilfe der Kammwachstumsreaktion. Arch. f. d. ges. Physiol. **229**:763-786, 1932.
24. Ogato, A.; Hirano, S., and Tanaka, S.: Über Auswertung des männlichen Sexualhormons nach der Fahnenkamm-Methode. J. Pharmaceut. Soc. Japan **54**:49, 1934.
25. Butenandt, A., and Tscherning, K.: Über Androsteron, ein krystallisiertes männliches Sexualhormon. Ztschr. f. physiol. Chem. **229**:167, 1934.
26. Greenwood, A. W.; Blyth, J. S. S., and Callow, R. K.: Quantitative studies on response of capon's comb to androsterone. Biochem. J. **29**:1400-1413, 1935.
27. Fussgänger, R.: Mechanism of the action of the male hormone. Medizin u. Chemie **2**:194-204, 1934.
28. Dessau, F.: Über die Zufuhr männlicher Hormone beim Kapaun durch Aufbringen auf den Kamm. Acta brev. Neerland. **5**:139-143, 1935.
29. Dessau, F., and Freud, J.: Effects of pure crystalline male hormones upon the comb of the capon and the ductus deferens. Acta brev. Neerland. **6**:9-11, 1936.
30. Deanesly, R., and Parkes, A. S.: Factors influencing effectiveness of administered hormone. Proc. Roy. Soc., London, Series B. **124**:279-298, 1937.
31. Callow, R. K., and Deanesly, R.: Effect of androsterone and of male hormone concentrates on accessory reproductive organs of castrated rats, mice and guinea-pigs. Biochem. J. **29**:1424-1445, 1935.
32. David, K.; Dingemanse, E.; Freud, J., and Laqueur, E.: Über krystallinisches männliches Hormon aus Hoden (Testosteron), wirksamer als aus Harn oder aus Cholesterin bereitetes Androsteron. Ztschr. f. physiol. Chem. **233**:281, 1935.
33. Freud, J.; Dingemanse, E., and Polak, J.: Assay of co-substance X of male hormones. Acta brev. Neerland. **5**:179, 1935.
34. Miescher, K.; Wettstein, A., and Tschopp, E.: On the activator of testosterone. J. Soc. Chem. Ind. **55**:238, 1936.
35. Zimmermann, W.: Eine Farbreaktion der Sexualhormone und ihre Anwendung zur quantitativen colorimetrischen Bestimmung. Ztschr. f. physiol. Chem. **233**:257-264, 1935.
36. *Idem:* Colorimetrische Bestimmung der Keimdrüsenhormone. Ztschr. f. physiol. Chem. **245**:47-57, 1936.
37. Wu, H., and Chou, C. Y.: Colorimetric methods for determination of sex hormones in human urine. Chinese J. Physiol. **11**:413-427, 1937.
38. Oesting, R. B.: Colorimetric assay for male sex hormones in urine. Proc. Soc. Exper. Biol. & Med. **36**:524-526, 1937.
39. Oesting, R. B., and Webster, B.: Sex hormone excretion of children. Endocrinology **22**:307-314, 1938.
40. Callow, N. H.; Callow, R. K., and Emmens, C. W.: Colorimetric determination of substances containing grouping $-CH_2 \cdot CO$ in urine extracts as indication of androgen content. Biochem. J. **32**:1312-1331, 1938.
41. Friedgood, H. B., and Gargill, S. L.: Biochemical and clinical studies of virilism before and after removal of adrenal cortical tumor. J. Clin. Investigation **17**:504, 1938.
42. Glass, S. J., and Bergman, H. C.: Subclinical adrenogenital syndrome. Endocrinology **23**:625-629, 1938.

ENDOCRINOLOGY AS NOW PRACTICED*

ROBERT T. FRANK M.D.†

NEW YORK CITY

TODAY every practitioner of medicine is forced and likes to practice endocrinology. I shall act as commentator of the current methods of treatment, and give you my own views, based on both clinical and laboratory experience. The most expeditious method of covering the subject will be to take up seriatim the symptoms produced by underfunction and overfunction of each gland, with short remarks on the treatments used, their effectiveness and limitations.

ANTERIOR PITUITARY GLAND

Underfunction. Before the adult stage has been reached, underfunction produces either the short, obese, Fröhlich type or the doll-like Levi-Lorraine syndrome, as well as the true pituitary dwarf. Anterior pituitary extracts have been used. No extract potent for the human being, either growth-promoting, maturizing or gonadotropic, is available. I have obtained no results by therapy in any of these groups. Many individuals develop into normal adults spontaneously. In the adult, Simmond's disease is produced by failure of anterior pituitary function. Death alone clinches the diagnosis, and no treatment has proved effective. The majority of recoveries occur in cases in which the disease is simulated, usually those of anorexia nervosa. It is conceivable that minor grades of the disease may exist, producing an asthenia similar to that seen with failure of the adrenal cortex. In these cases, if no improvement is produced by a potent cortical extract, Simmond's disease must be suspected.

Overfunction. Excessive growth is produced in the adolescent group. Giants in the adolescent group suffer because their school contacts are rendered difficult by their excessive size, which is disproportionate to their mental attainments. My efforts to control the rapidity of growth by large doses of androgens in girls and estrogens in the youths have shown no results. X-ray therapy to the pituitary gland, which has been advocated, is too dangerous for me to attempt it. In the adult group, acromegaly is a chronic disease when first seen, and has proved unresponsive to every form of treatment except surgical intervention to save eyesight.

*Presented at the New England Postgraduate Assembly, Cambridge, November 15, 1938.

†Clinical professor of gynecology, Columbia University College of Physicians and Surgeons; consultant gynecologist, Mount Sinai Hospital, New York City.

POSTERIOR PITUITARY GLAND

Diabetes insipidus, characterized by excretion of 5 to 20 liters of urine per day, is due to a disturbance of the posterior pituitary lobe, sometimes caused by pressure on the hypothalamus. This condition is controlled by appropriate doses of posterior pituitary extract, given by hypodermic injection, under the tongue or intranasally. Intermedin shows no advantages over posterior pituitary extract.

THYROID GLAND

Thyroid disturbances are sufficiently understood, and require little discussion.

Underfunction. Cretins, if taken in hand sufficiently early, can be developed into fairly normal individuals. Adults with myxedema can be kept in normal health by desiccated thyroid gland or thyroxin. It must be remembered that the several thyroid preparations vary greatly in strength, and it is well to become acquainted with and stick to one preparation. Thyroid underfunction may produce many by-effects, such as amenorrhea, obesity or abortion. In adolescents, severe menorrhagia is sometimes noted.

Overfunction. Endemic adolescent goiter no longer forms a public-health problem, thanks to Marine's iodine mass therapy. Patients with exophthalmic or toxic goiter, particularly those with a mild degree of the disease, respond to medical measures, particularly to a placid and protected form of life. For the present, at least, most cases remain largely surgical problems. The use of x-ray for the treatment of this condition is risky, for the dose is almost impossible to gauge, and regression is apt to continue for a long time after the treatment has been stopped, with resultant underfunction.

PARATHYROID GLAND

Underfunction. If underfunction is acute, tetany is readily relieved by calcium, fluids and parathormone. Chronic tetany, oftenest seen as the result of surgical removal of the parathyroids, shows increasing tolerance to parathormone, and this makes effective relief difficult. Whether the dihydrotachysterol introduced by Holtz will permanently replace parathormone in these patients is as yet undetermined.

Overfunction. Hyperparathyroidism is due to parathyroid adenoma and produces osteitis fibrosa cystica. It is believed that both scleroderma and osteomalacia are likewise due to parathyroid overfunction. Surgical intervention is indicated, with removal of the adenoma, and sometimes of parathyroid tissue where diffuse hyperplasia appears to exist.

PANCREAS

Underfunction. Pancreatic insufficiency causes diabetes mellitus. This disease has been robbed of much of its gravity by the discovery of insulin. I shall not venture to discuss the use of insulin here in the vicinity of Boston, but it should be appreciated that cases difficult to control require special knowledge.

Overfunction. Hyperinsulinism, with its dramatic and often misleading train of symptoms, — particularly convulsions, — is due to adenoma of the islands of Langerhans. Surgical intervention is called for if the diagnosis is well established. At laparotomy the adenomas may not be discovered, and even at autopsy the multiple small nodules may be difficult to recognize.

ADRENAL GLANDS

Underfunction. Addison's disease, due in the vast majority of cases to tuberculosis of the adrenal cortex, proves fatal unless adequate amounts of potent cortical extract are administered. The commercial extracts vary in potency and appear to deteriorate, and are therefore rarely effective. Minor degrees of insufficiency most probably produce severe asthenia and loss in weight, the syndrome then resembling minor grades of Simmond's disease. Such patients should be benefited by a potent cortical extract.

Overfunction. Overgrowth of the adrenal cortex produces the adrenocortical syndrome. The underlying condition may be carcinoma or hyperplasia. The resulting complex is marked by hirsutism, trunk obesity, polycythemia, high blood pressure, osteoporosis and colored striae. If visualization of the adrenals by means of perirenal insufflation of carbon dioxide shows enlargement, surgical removal of the tumor or resection of the hyperplasia is indicated. As the operation is difficult and dangerous, it is not yet advised for minor degrees of the syndrome.

Overfunction of the adrenal medullary produces extreme hypertension. If such a condition is diagnosed, surgical removal of the paraganglioma is indicated.

Hirsutism, particularly facial hirsutism in women, appears to be due to an adrenal disturbance. Large doses of estrogen have not produced any improvement. Bleaching of the hair and electrolysis appear at the moment to be the sole remedies for this very disturbing disfigurement.

MALE GONADS

Underfunction. In the adolescent group hypogonadism, because of the accompanying growth

disturbances, appears almost assuredly a primarily pituitary underfunction. These boys are usually tall and obese, and not infrequently show gynecomastia. The testes are very small, with correspondingly small phallus and prostate. The disturbance is usually noted about the tenth or twelfth year. Often but not invariably cryptorchidism is present. No operative intervention for the latter should be undertaken until at least a year's treatment with the gonadotropic factor, obtained from pregnancy urine, has been tried. This factor, however, does not relieve hypogonadism. The great majority of these adolescents eventually become normal by the nineteenth or twenty-first year. Less than 5 per cent are permanently handicapped. Pituitary glandular extracts are of no avail. If the thyroid function is insufficient, thyroid extract may be given. Androgens are not indicated. Adult hypogonadism cannot be cured. Libido may be temporarily awakened by adequate dosage of androgens in both hypogonad individuals and castrates. At least 25 mg. of testosterone, given two or three times a week, is required. No permanent good is achieved by this therapy, and the effect is undoubtedly psychic. Spermatogenesis is not stimulated.

Overfunction. In adolescent males hypergonadism is a very rare syndrome. I have seen it as early as the sixth year, with full hirsutism, large phallus, strong sex urge and disturbed or defective mentality. These individuals are liable to be arrested for sex delinquencies or crimes. The underlying cause appears to be adrenal hyperfunction. If an enlargement of the adrenal is diagnosable, surgery is indicated, and even if not demonstrated, exploration is justified. The attempt to produce reduction of prostatic hypertrophy with androgens does not rest on a sound basis, and the effects reported are not convincing.

FEMALE GONADS

Underfunction. Such a condition is not recognizable until the normal time of pubescence. As in the male, the build is usually abnormal, either infantile or eunuchoid. The secondary sex characteristics do not develop. Menstruation does not appear. As the time of menarche is very variable, too early efforts at treatment are to be avoided. This condition is primarily due to prepituitary underfunction. It cannot be influenced by direct measures. The gonadotropic extracts derived from pregnancy urine do not help. Thyroid underfunction demands thyroid extract. Estrogens are of no use. Obesity or malnutrition, both frequent causes, should be corrected by adequate hygienic and dietary measures.

In adults, both primary and secondary amenorrheas, unless due to thyroid insufficiency, obesity, malnutrition or some severe intercurrent constitutional disease, such as tuberculosis, are unresponsive to any form of treatment, the condition almost surely being due to primary prepituitary insufficiency. Huge doses of estrogen (1,500,000 international units) are required to produce a single menstruation, a result which is of little benefit to the patient. Frequently without known cause, menstruation and fertility return after many years of amenorrhea. Likewise conception during a long period of amenorrhea is sufficiently frequent to require mention. Small doses of x-ray to the ovarian regions have restored menstruation and fertility, but in my opinion more cases have been rendered permanently amenorrheic and sterile by this form of therapy.* Recently, intravenous injection of pregnant mare's serum has produced ovulation and has been followed by pregnancy. The potential dangers inherent in this method of treatment limit its application to very expert hands.

The menopause (both physiologic and that induced by x-ray therapy or by surgical castration) is the most extreme form of underfunction. All its symptoms, — mental, neurovascular, arthritic and digestive, — as well as local atrophies, are relieved by adequate dosage of estrogens. The therapy must be continued at intervals for a long time. Estrogens are specific for the relief of the symptoms of the menopause.

Overfunction. Hypersecretion of the ovaries is due to prepituitary overfunction. In the majority of cases, menorrhagia and metrorrhagia are the predominant symptoms. It is necessary to exclude anatomic causes for the bleeding, such as cervical lesions, carcinoma and fibroids. Hyperplasia of the endometrium and, if the condition exists for a long time, of the uterine muscle results. In my hands the gonadotropic factors, estrogens as well as androgens, have proved ineffective. Just as in all the other hyperfunctional conditions, surgery is indicated. As a rule, curettage in older patients, followed by intrauterine radium or by x-ray therapy applied to the ovaries, must be resorted to. In the adolescent group, as previously mentioned, 20 per cent show marked hypothyroidism with basal metabolic rates as low as —35 per cent. Thyroid therapy cures these cases. Where the thyroid function is normal, subcutaneous injection of moccasin venom has proved effective, although relapses are frequent, requiring resumption of the treatment.

*This type of radiotherapy requires accurately graduated dosage. If it is to be employed it must be limited to fully qualified specialists.

* * *

At present the vast majority of overfunctions of any of the glands of internal secretion warrant surgery if the diagnosis can be made. However, in my experience at least 50 per cent of the patients sent to me as having endocrine disease have been found to be suffering from non-endocrine conditions. I therefore emphasize that the search for non-endocrine causes must not be neglected. Only if such causes cannot be found should an endocrine origin be suspected.

In spite of the huge number of so-called endocrine products available, comparatively few are actually potent. The use of anterior pituitary powder and of mammary, placental, splenic, thymic, pineal and orchitic extracts, foisted on the profession by alluring clinical reports, and reappearing in even more attractive form in some of the pharmaceutical literature, are entirely unjustified. On the other hand, no one can doubt the physiological and clinical value of thyroid extracts, parathormone, estrogens, androgens and potent adrenocortical extract. Their effects on properly selected cases are too specific and indubitable to be overlooked or misinterpreted.

1035 Park Avenue.

UNILATERAL RENAL DISEASE WITH ARTERIAL HYPERTENSION*

Report of a Case Apparently Cured Following Nephrectomy

J. Dellinger Barney, M.D.,† and Howard I. Suby, M.D.‡

BOSTON

IN VIEW of the rapidly increasing interest in the association of unilateral renal disease with long-continued arterial hypertension, we report in detail the history of a patient with this interesting combination of circumstances.

L. F. F., a 10-year-old, white, American girl, entered the Urological Service of the Massachusetts General Hospital through the Emergency Ward on March 16, 1937, complaining of right midabdominal pain of 1 week's duration. The onset was sudden; the pain was steady, dull and non-radiating, and was located below and to the right of the umbilicus. There was no accompanying nausea, anorexia or urinary or bowel symptoms. About 48 hours later an exacerbation of this pain "doubled her up." There was still no nausea or vomiting, and the bowels moved after a cathartic. Next day the patient felt much better. Three days before entering the hospital there was another exacerbation of pain, intensified on leaning forward. Subsequent to this an ice bag was applied to the abdomen and a cathartic, followed by an enema, was given.

The patient was said to have had "pyelitis" 3 years previously; about 2 months previously she had had an attack of burning on urination, but this was apparently of brief duration. She had always been constipated, undersized and undernourished. The family history was irrelevant except that the mother at the time of the patient's entry was ill with pleurisy.

Examination showed a well-developed but undernourished, sallow child, lying in bed in no apparent distress. The throat was moderately injected, the teeth neglected. The heart and lungs were negative. Abdominal examination showed tenderness and spasm localized over a small area to the right of and below the umbilicus. There was so much muscular spasm that it was difficult to palpate the region of the right kidney. There was no costovertebral tenderness, and no organs or masses could be felt. Peristalsis was normal; there was no psoas spasm; rectal examination was negative. The blood pressure was 185/130, the temperature 99°F., and the pulse and respirations were normal. On admission the urine was acid; there was a very slight trace of albumin but no bile, sugar, acetone or diacetic acid. The sediment showed 10 to 20 white cells per high-power field. Subsequent urinalyses showed the same findings.

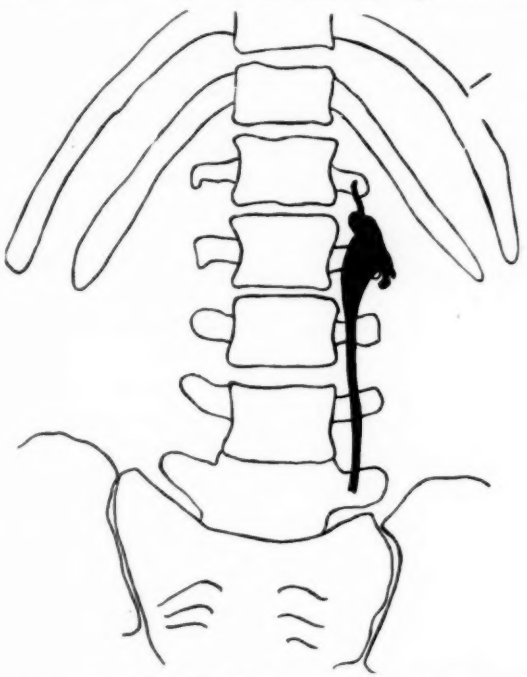

FIGURE 1. *Tracing of Right Retrograde Pyeloureterogram.*

Blood studies showed 4,710,000 red cells, a hemoglobin

*From the Urological Department, Massachusetts General Hospital.
Read at a meeting of the New England Surgical Society, Boston, September 20, 1938.

†Member of Board of Consultation, Massachusetts General Hospital.

‡Urological resident, Massachusetts General Hospital.

of 70 per cent and from 9500 to 12,500 white cells; the differential was normal. The nonprotein nitrogen was 20 mg. per 100 cc.; the phenolsulfonephthalein excretion was 61 per cent in 2 hours. A blood Hinton test was negative, as was a von Pirquet test. The stool was negative to guaiac.

Roentgenograms of the urinary tract showed the left kidney to be normal in size and position; the right kidney could not be visualized, perhaps because of gas and fecal matter in the colon. An intravenous pyelogram showed good excretion of the dye on the left with a normal pelvis, calices and ureter; no dye was excreted by the right kidney. The findings were regarded as indicative of a non-functioning right kidney. Plates of the chest were essentially negative.

Cystoscopic examination showed normal bladder and ureters. Catheters were passed without difficulty to either kidney. No urine whatever was obtained from the right; that on the left showed no leukocytes. The bladder urine showed 1 to 3 leukocytes per high-power field. A culture of the bladder urine was sterile on one occasion and later showed *Bacillus coli;* the left-kidney urine was sterile. A right retrograde pyelogram was done, about 3 cc. of Skiodan being injected. This showed poor filling of the minor calices; the pelvis did not appear to be dilated. (Fig. 1.)

Subsequently the patient was seen in consultation by various members of the Pediatric Service. It was the consensus of all that we were dealing with an atrophic, functionless and probably infected right kidney. This, together with the fact that several blood-pressure readings showed persistent hypertension, the figures varying from 185/130 to 200/170, led to the opinion that the case was probably one of hypertension resulting from unilateral renal disease and that nephrectomy was indicated.

At operation on March 31 (by J. D. B.), an oblique incision was made in the right loin. A kidney about one quarter normal size was found lying in a normal position. It was quite firm and fibrous, and not adherent. There were no abnormal vessels noted, and the pelvis and ureter looked normal. The kidney was removed without incident. A drain was placed in the depths of the wound, which was then closed around it in layers.

The pathological report gave a diagnosis of healed pyelonephritis with renal atrophy, and was as follows:

> Gross examination shows a kidney measuring 5 by 2 by 1 cm. The surface is smooth, pinkish-gray and glistening. On section the kidney substance measures 1 mm. in thickness and is soft. The pelvis is dilated. The mucosa is grayish, smooth and glistening. The ureter measures 4 cm. in length and is slightly injected but otherwise negative.
>
> The vessels appear normal but quite small. Immediately beneath the epithelium in one calyx is an extensive infiltration of lymphocytes, mononuclears, and occasional eosinophils. Other scattered foci of lymphocytic infiltration are found throughout the organ. Sometimes there is follicle formation. No abscesses are present. The parenchyma shows extensive atrophy, with sclerosis of many glomeruli and marked tubular atrophy. Throughout the kidney marked vascular changes are present, consisting chiefly of intense thickening in the smaller arteries and arterioles. This is most marked in the areas of parenchymal atrophy, but is not limited to them. The cause of the renal atrophy cannot be determined with certainty, but the picture is consistent with a burned-out pyelonephritis. (Fig. 2.)

Convalescence from operation was brief and uneventful. Twenty-four hours later the blood pressure had dropped to 110/70, at about which point it remained until she was discharged. While in the hospital after operation, a few pus cells were found in the urine and a culture showed *B. coli*. After the patient was put on an acid-ash diet and mandelic acid the urine became pus-free and sterile, and has remained so ever since.

FIGURE 2. *Photograph of Kidney Cortex.*

During the 21 months since operation the patient has been seen at frequent intervals and the blood pressure has been checked. The systolic pressure has been a little over 100, but the last reading, taken on December 7, 1938, was 98/60.

From the time of Bright[1] it has been realized that certain forms of cardiovascular disease in man cause pathologic changes in the kidney and that hypertension may be the result of diffuse vascular disease with kidney involvement. Fahr[2] regards hypertension as a compensatory phenomenon to offset the reduced blood flow through the diseased kidney. Volhard and Suter,[3] however, believe that there is a humoral mechanism of renal origin as a cause of hypertension. From a review of the literature it seems obvious that even those who regard certain cases of hypertension as of renal origin cannot explain its mechanism.

Various experimental procedures, all aimed at producing an elevation of blood pressure, have been carried out in animals. These have given

varied but not constant results. Goldblatt[4] and his co-workers have done what is perhaps the most convincing work in this direction. By partial occlusion of the renal arteries with a silver clamp they were able to produce a renal ischemia accompanied by hypertension. Their experiments indicate that at least experimental hypertension is due primarily to a humoral and not to a nervous mechanism. While the exact nature of the effective humoral substance has not yet been determined, it seems probable that it works in conjunction with the adrenocortical hormone in the production of hypertension in man.

In connection with the case which we have reported, it is interesting, perhaps valuable, to review the cases of unilateral renal disease occurring on the Urological Service at the Massachusetts General Hospital. Beginning with 1911 we have reviewed to date the records of all such cases with a diagnosis of pyonephrosis, pyelonephritis, hydronephrosis or pyelitis. There was a total of 305, of which 224 were nephrectomized. Women outnumbered men, 171 to 134. Seventy-six cases, or 25 per cent, had hypertension — a preoperative systolic blood pressure of at least 140 mm. of mercury. Since Cabot[5] regards 110 to 135 mm. as the normal range of systolic blood pressure, we have arbitrarily taken pressures of 140 mm. or higher as evidence of hypertension but realize that this figure may be questioned.

It is obvious that an investigation of this kind in order to be of value should include a complete follow-up. Unfortunately for our present purpose, the importance and value of taking postnephrectomy blood-pressure readings have but just been realized; and although many of the patients, whether or not operated on, were seen in the clinic at varying times after leaving the hospital, the blood pressures were taken in but 15 cases.

Of these patients, all of whom were nephrectomized and seen from four months to nine years after operation, 10, or 67 per cent, showed an average drop in systolic pressure of 30 mm., as compared with the preoperative level.

COMMENT

We consider the case reported to be an unusual example of unilateral renal disease, associated with and probably causing hypertension, and cured for twenty-one months by nephrectomy. There are few if any similar cases which have been closely observed for this length of time after operation.

We do not wish to put undue stress on the investigation of the cases from the Urological Service. It seems to us, however, that it indicates the importance of carefully studying and following up cases of unilateral renal disease, especially from the point of view of hypertension, both before and after operation. This procedure may result in the discovery that so-called renal hypertension is commoner than we have supposed.

REFERENCES

1. Bright, R.: Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. Guy's Hosp. Rep. 1:338-379, 1836.
2. Fahr, T.: Pathologische Anatomie des Morbus Brightii. *Handbuch der Speziellen Pathologischen Anatomie und Histologie.* 758 pp. Berlin: Julius Springer, 1925. Pp. 156-472.
3. Volhard, F., and Suter, F.: Nieren und ableitende Harnwege. *Handbuch der inneren Medizin.* 1023 pp. Berlin: Julius Springer, 1931.
4. Goldblatt, H.: Studies on experimental hypertension; pathogenesis of experimental hypertension due to renal ischemia. Ann. Int. Med. 11:69-103, 1937.
5. Cabot, R. C.: *Physical Diagnosis.* Fifth edition. 540 pp. New York: William Wood & Co., 1912.

REPORT ON MEDICAL PROGRESS

DIAGNOSTIC ROENTGENOLOGY

RICHARD SCHATZKI, M.D.*

BOSTON

ROENTGENOLOGY is a field which is so intimately connected with most other specialties that advances in any of the latter naturally stimulate progress in the former, and conversely, developments in roentgenology favorably influence the other specialties. Progress in diagnostic roentgenology is commonly due to the introduction of new methods, but a different use of established types of examination often produces essential diagnostic improvements. Slight changes in the appearance of a roentgenological picture, recognized for many years and thought to be unimportant, after intensive study directed to this particular point, at times prove to be the only visible sign of an important pathologic lesion. On the other hand, small variations may have been overlooked for decades before being described. Examples of advances due to changes both in method and in interpretation present themselves in the review of recent progress in diagnostic roentgenology.

HEART

For many years it has been a dream of roentgenologists and cardiologists to be able to see not only the comparatively undifferentiated shadow of the outside of the heart but also the shadow cast by the heart chambers themselves. In recent years, roentgenological studies of intracardiac calcifications (calcified valves, calcified annulus fibrosus, and so forth) and their movements have shown how complicated the physiology of the interior of the heart is and how little we know about it. (Sosman and Wosika.[1])

These investigations only increased the hope that a method of exploration of this roentgenological *terra incognita* might be found. After unsuccessful attempts by many authors, Robb and Steinberg[2] in 1938 succeeded in obtaining pictures of the inside of the hearts of living men. By rapidly injecting approximately 35 cc. of 70 per cent Diodrast — the non-radioactive organic iodine compound which is routinely used in weaker concentration for intravenous pyelography — into the cubital vein, they obtained radiographic pictures of the following structures: the superior vena cava and its tributaries, all four heart chambers, the ventricular walls, the interventricular septum, the tricuspid, pulmonic and aortic valves, the pulmonic and aortic sinuses, the pulmonary arteries and the thoracic aorta. The flow of the dye was so rapid that not all these structures were seen simultaneously, and preceding tests (ether test, cyanide test) were necessary in order to determine the optimal moment of radiographic exposure for a certain structure in a given patient.

The experience of these authors suggests that the method is not dangerous. It is not yet possible to obtain consistently a picture of any part of the cardiopulmonary circulation desired and failures are to be expected. In principle, however, the method has solved the above-mentioned problems, though improvements are necessary and are to be hoped for. The value of this method for the study of the physiology and pathology of the chest is obvious. Its prospects of becoming important in clinical medicine are excellent.

It will be helpful in many ways, such as in the differentiation of rheumatic and congenital heart lesions, in the differential diagnosis of mediastinal tumors and aneurysms, in the study of venous flow in constrictive pericarditis and in the determination of locus and cause of obstruction in upper mediastinal syndrome.

PULMONARY DISEASES

Considerable progress has taken place in recent years in the roentgen examination of pulmonary diseases. This progress is characterized by the recognition of the role which mechanical factors play in roentgenological changes. Instead of describing "shadows," roentgenologists have become interested in the mechanical factors causing them; in other words, the parenchymal changes are studied as secondary to those in the bronchi and vessels. Obstructing lesions of the bronchi may produce atelectasis or, by a ball-valve mechanism in less complete cases, localized emphysema of the involved lung segment. Changes in the position of the diaphragm and mediastinum, as well as variations in the size and position of the hilar shadows, commonly occur. Secondary pneumonic and purulent processes with bronchiectasis and cavity formation may take place in the atelectatic areas.

Of course, not all pathologic changes can be

*Instructor in roentgenology, Harvard Medical School; roentgenologist, Massachusetts General Hospital.

explained on this basis. But the stress laid by authors[3–5] in various countries on the study of these mechanically produced changes has resulted in the explanation of a number of patterns in the x-ray films of the lungs, the origin of which had not been known hitherto. For instance, horizontal lines in the lower lung fields were found to be due to small, plate-like areas of atelectasis (Fleischner[4]): again, so-called pictures of interlobar effusion were found to be produced by atelectasis (Hampton and King[5]).

This newer viewpoint made possible the recognition of the etiologic factor in cases of severe one-sided pulmonary disease, for example bronchial obstruction due to benign adenoma with secondary complete destruction of one lung. It decreased the number of lesions which had been erroneously called tuberculosis. More important, it led to the correct diagnosis in cases in which a small bronchial tumor or bronchial tuberculosis had produced bronchiostenosis with changes in the x-ray picture — variations which might readily escape the attention of an examiner unfamiliar with these studies. A slight displacement or a decrease in size of a hilar shadow, or a localized area of emphysema, for instance, might be the only abnormality visible in such a case. In addition these studies have decreased the number of so-called negative x-ray films in cases with hemoptysis.

The causes of bronchial obstruction are numerous: mucus, blood, foreign body, tumor, tuberculous and other inflammatory disease of the bronchial wall, pressure from outside by large lymph nodes, mediastinal tumor or aneurysm. The x-ray examination without contrast substance can often lead only to the diagnosis of bronchial obstruction and its location, whereas the etiology has to be established by clinical examination, bronchoscopy or lipiodol examination of the bronchi.

The progress in roentgenological examination of the chest is a characteristic example of the beneficiary effect of co-ordination of medical specialties. Advances in thoracic surgery have allowed operative control in many previously unsolved cases. They tremendously stimulated interest and therewith progress in thoracic roentgenology, the results of which in turn were used for the problems of thoracic surgery.

Hampton and Castleman[6] studied pulmonary embolism and infarction by comparing postmortem teleroentgenograms with the pathologic findings within lungs which had been distended by formalin to their normal size. They found that infarcts were more often visible on films than had been assumed. They were always subpleural, were particularly frequent in the lung edges and had a characteristic roentgenologic appearance. Though the infarct usually decreased in size gradually and healed with scar formation, these authors have seen cases with rapid resolution of the x-ray shadow without necrosis or scar formation (incomplete infarct). The incidence of embolism and infarcts in nonsurgical and in noncardiac cases without clinical evidence of phlebitis was striking. The roentgenological recognition of pulmonary embolism without infarction has been made only in exceptional cases in which extensive embolism was followed by thrombosis of the pulmonary arteries and the formation of a cor pulmonale. Usually such embolism is thought to produce no roentgenologic changes. It is therefore of great interest to note that Westermark[7] described segmental pulmonary anemia, resulting in a narrowing of the lung vessels and localized increased brightness, as a sign of pulmonary embolism.

GASTROINTESTINAL TRACT

Within the last decade, roentgenology of the gastrointestinal tract has gone through a developmental stage which should be reported briefly, even though no unusual contribution has been made within the last year. This development, which started in various countries, and the main banner-bearers of which were Forssell[8] and Berg,[9] did not appear in this country until rather recently. It is characterized by the stress laid on the demonstration of the inner relief of the organs of the gastrointestinal tract. A barium coating is applied, thin enough to leave the elevations of the inner surface free while the valleys are filled. An x-ray examination at this stage of filling shows a picture of the relief of the whole inner surface of the organ, not only a shadow of its mass. In addition, a technical improvement has been developed which allows taking pictures during fluoroscopy, thus permitting the exact instantaneous fixation of a fluoroscopic image (so-called "spot" or aimed film).

This new orientation has led to the roentgenological demonstration of esophageal varices, and hence to the diagnoses of cirrhosis of the liver and of thromboses of the portal and splenic veins, and the differential diagnosis of splenomegaly has been markedly improved. The etiology of hematemesis has been established in many cases by the demonstration of varices. More commonly than before, small lesions, particularly tumors of the stomach and colon, are discovered roentgenologically and small ulcers in unusual positions are demonstrated. The high frequency and exactness with which the actual ulcer crater is demonstrated allow one to differentiate the ulceration itself and cicatricial

processes produced by the ulcer, and to decide, more frequently than before, whether or not an ulcer is active.

This technic has enabled the roentgenologist to show changes in some cases of gastritis. Above all, the roentgenological diagnosis of lesions of the gastrointestinal tract has been put on a more secure basis. The films obtained by this method represent the optimal fluoroscopic picture, so much so that they allow the study of the fluoroscopic image to continue without the patient's being present, and thereby make the diagnosis more certain in difficult cases. Except for color it is possible to obtain a picture of the inner surface of the gastrointestinal tract comparable to that which the pathologist sees when he looks at the opened specimen.

Ulcerated lesions which, owing to the changes in the vicinity of the ulcerations, are clearly malignant on inspection can be recognized as such roentgenologically. The differentiation of benign ulcers and those which grossly appear to be benign, but prove to be malignant histologically, still defies the efforts of any macroscopic type of examination, including roentgenology.

GALL BLADDER

Roentgenological examination of the gall bladder has a fair percentage of failures. Usually, the failure is due to the fact that small stones, due either to respiratory or pulsatory motion or to the small size of the stones compared with the density of the overlying dye, are not visible within a dye-filled gall bladder. Recent technical and methodical developments have tended to decrease the number of these errors.

One definite advancement has been the introduction of the examination of the dye-filled gall bladder in the upright position (Akerlund,[10] Bernstein,[11] Ettinger[12]). Since most stones sink to the bottom of the gall bladder in this position, they are crowded in a small space at the fundus and are therefore more easily recognized than on films taken with the patient in the usual prone position, and overlying gas shadows can be more easily differentiated. The peculiar phenomenon of stones floating at a certain level in the dye has been described by these authors and has been confirmed by others. This examination is particularly valuable if done under fluoroscopic control.

A remarkable technical development is the construction of x-ray tubes with a rotating anode. In such a tube, the heat developing in the focal spot of the anode is distributed over a large area, and the use of a small effective focal spot together with a large load given in a fraction of a second is possible. In the resulting films, excellent definition is present, and small biliary concretions are demonstrable with greater regularity than they have been heretofore.

SPINAL CANAL

It was a definite step forward when Camp[13] reported that slight pressure defects of the bony spinal canal produced by lesions, usually tumors, could be demonstrated. Unless the tumor was big, however, a diagnosis from the flat film was possible only when the tumor was localized in a favorable position. An examination following intradural injection of a contrast substance was therefore still necessary in many cases of intraspinal lesions. For this purpose Lipiodol remains the most reliable substance. The examination of small lesions of the spinal canal with this contrast medium has been markedly improved, with resulting discovery of characteristic pictures in posterior rupture of the intervertebral disks (Hampton and Robinson[14]). The fluoroscopic examination of the Lipiodol-filled spinal canal approaches that of the gastrointestinal canal in accuracy. But unless removed during operation, the Lipiodol remains indefinitely in the dural sac. In spite of this, the cases of permanent ill effects attributable to the presence of the oil are comparatively rare.

In a search for a more inert contrast substance, Young and Scott,[15] among others, have advocated the use of a gas. They were able to demonstrate even small ruptured disks after the introduction of air in the dural sac. Other examiners have not been so successful. It is advisable, however, to try an air examination of the spinal canal in cases of block before resorting to Lipiodol. The ideal contrast substance for the examination of the spinal canal has not yet been found, and therefore exact indications must be present before the present substances are employed.

ENCEPHALOGRAPHY AND VENTRICULOGRAPHY

In recent years the frequency with which air has been introduced into the cranial cavity for the study of non-neoplastic intracranial lesions has constantly increased, while there is a general tendency to decrease, if possible, the number of air injections in patients with questionable brain tumor. The intensive efforts of making a correct diagnosis and localization from the clinical findings, the electroencephalogram and a careful study of the flat films of the skull are, however, successful only in a comparatively small group of patients. In the large majority of cases an examination after intraventricular or intralumbar injection of air is still necessary. While no revolutionary changes

have taken place in the method or interpretation of cerebral air injection, the appearance of excellent summarizing reports on the normal encephalogram (Davidoff and Dyke[16]) and the pathologic ventriculogram (Lysholm et al.[17]) is worth reporting.

SOFT TISSUES

Roentgenology of the soft tissues is based on a fundamental principle. In respect to x-rays, air is less dense than fat, and fat less dense than the rest of the soft tissues of the body, all the latter being of comparatively equal density. The extensive distribution of fat in fascia and in other parts of the body produces enough contrast to give shadow pictures of muscles and internal organs. Carty[18] in particular emphasizes the importance of the resulting pictures. Edema produces a fairly characteristic pattern, the early recognition of which may be helpful in the diagnosis of inflammatory disease. This technic is of particular help in the diagnosis and differential diagnosis of soft-tissue tumors. The size, the shape and, when present, the capsule of a tumor can be visualized. Lipoma and hemangioma produce almost pathognomonic pictures, the former by the radiolucency of the tumor, the latter by its wormlike structure. The results obtained in the diagnosis of cancer of the breast from such an examination have, as a whole, been rather disappointing. On the other hand, soft-tissue films have become a routine procedure in the diagnosis and treatment of tumors of the pharynx and larynx.

In order to improve the results of the roentgenography of soft tissues, Gratz[19] recommended the intrafascial injection of air. Although this procedure may be of help in some cases, it is usually not necessary.

PLACENTA PREVIA

A few years ago, Ude and Urner[20] devised a roentgenological method of diagnosing placenta previa. They injected a small amount (25 to 40 cc.) of a contrast substance, for example sodium iodide, into the bladder. The distance between the inner wall of the bladder and the presenting head of the fetus is normally not more than 1 cm.; in placenta previa, however, it is greater. Recent reports from other authors[21] confirm these observations. The main value of the method seems to lie in the exclusion of placenta previa. Erroneous positive diagnoses may be due to blood clots or presenting soft tissues, but are said to be avoidable if the whole clinical picture is taken into careful consideration. Even though the fetal head and bladder may have a normal relation by x-ray examination, placenta previa may exist on the posterior wall of the uterus behind the head.[22] The results of this type of examination have therefore to be accepted with reservation.

CONTRAST DEMONSTRATION OF LIVER AND SPLEEN

Ten years have passed since Radt[23] and Oka[24] discovered that colloidal thorium dioxide (Thorotrast), when injected intravenously, accumulated in the reticuloendothelial cells of the liver and spleen, thus allowing a roentgenological demonstration of these organs. The potential danger of the radioactivity of the injected substance immediately brought out protests against its use for diagnostic purposes. The time which has since elapsed allows us to evaluate better the arguments pro and con. There is no doubt that Thorotrast remains in the body almost indefinitely; for example, five years after injection 27 per cent of the substance has been found in the liver alone.[25] Several reports showed, though not absolutely convincingly, evidence of late damage, such as fibrosis in the liver, spleen and adjacent organs.[26] The radioactivity of the amount of Thorotrast used was shown to approach that of minimal doses of radium which have been proved to produce chronic radium poisoning. Nevertheless, other authors[27] have stressed the absence of any demonstrable injury in a group of cases observed over a period of several years.

On the whole, there remained enough doubt in the minds of most roentgenologists to prevent the indiscriminate use of this substance for the demonstration of the liver and spleen. Furthermore, with the passage of time there is now less necessity for such a contrast demonstration. Ordinarily, the outlines of the liver and spleen can be recognized on good flat films of the abdomen. Finally, the differential diagnosis of questionable tumors in the left upper abdomen, as well as the diagnosis of cirrhosis of the liver, has been greatly improved by the roentgenological demonstration of esophageal varices. However, a nontoxic dye permitting the visualization of healthy liver parenchyma should be of great practical value, particularly in the search for liver metastases. It is therefore of interest that Beckermann and Popken[28] have recently succeeded in visualizing the liver and spleen by the intravenous injection of colloidal organic iodine compounds. These substances are not radioactive and are apparently nontoxic. If the preliminary report is confirmed, a new field for routine roentgenological examination seems to be opened up.

KYMOGRAPHY AND BODY-SECTION ROENTGENOGRAPHY

Among the roentgenological methods which have been introduced in recent years are two which require mention because they involve interesting technical procedures and because they have been widely discussed. They are kymography and body-section roentgenography.

Kymography is a method which demonstrates different phases of the motion of an organ on a single film. In order to get such a picture, a grid with several narrow slits is placed between the patient and the cassette. By moving the cassette during a comparatively long exposure, a record of the motion of those parts of the organ seen through the slits is obtained. In other words, the type, speed, rate and extent of motion can be studied roentgenologically on a single film. Stumpf[29] deserves the main credit for the development of this method, which has been introduced in this country by Hirsch[30] and Scott and Moore.[31] The procedure has been extensively used for the study of the heart and vessels, to a lesser degree for that of the lungs, diaphragm and gastrointestinal organs. It has proved of interest in scientific research, but its clinical value has been thus far limited to a small number of cases, those, for instance, in which cardiac aneurysms could be demonstrated, or in which a differentiation of mediastinal tumor and an aneurysm was made possible. Kymography offers an excellent way of obtaining a permanent record of motion of an organ if needed for later comparative studies.

The aim of body section roentgenography, or planigraphy, is the roentgenological demonstration of a certain plane of a body by blurring every shadow produced by parts of the body above and below this plane. The blurring effect is obtained by moving the tube and film during the exposure in such a way that the resting-point of the axis of this movement lies in the desired plane. Its shadow is therefore well defined while everything else is erased by motion.

The principle of this method is relatively old. Recent applications have been reported under various names — laminagraphy, planigraphy, tomography, x-ray focussing device, and so forth. In this country Kieffer[32] and Moore[33] have emphasized the importance of the method. The isolated demonstration of a tissue disk of 5-mm. thickness becomes possible. In the demonstration of areas difficult to examine, owing to dense overlying structures, for example the sternum or the sternoclavicular joint, the value of this procedure is obvious. In the study of pulmonary disease (studies of cavities, bronchi, and so forth) those who have used it praise it. Further use will show whether the method has general clinical value beyond the study of exceptional cases. The introduction of a simple planigraphic mechanism which can easily and without great expense be added to any Bucky table (Twining[34]) will probably popularize the method and allow its value to be judged on a broader base.

MOVING PICTURES AND PHOTOGRAPHY OF THE FLUOROSCOPIC SCREEN

A roentgenological record of the motion of the internal organs has been attempted for many years. More or less crude films were obtained by the use of revolving x-ray tubes and films (direct method) or by photography of the image on the fluoroscopic screen (indirect method). Recent improvements in fluoroscopic screens, photographic films and lenses have resulted in the production of roentgenological moving pictures of distinct value.[35, 36] Up to sixteen pictures can be taken per second, and even the fast-swallowing act has been recorded successfully. The teaching value of such a method is obvious. The same motion can be demonstrated to students again and again without endangering the patient. It is possible that diagnostic progress may also be obtained by this method.

The same improvements which allowed successful screen filming have made simple screen photography possible.[37] In other words, instead of using a large x-ray film one is able to photograph the screen image of a patient's chest on a small photographic film, and to study it directly or after magnification. Though such a method cannot be substituted for the routine methods of examination, its advantages in the examination of large groups of persons — soldiers, students, and so forth — are obvious.

REFERENCES

1. Sosman, M. C., and Wosika, P. H.: Position of heart valves and their relation to anterior chest wall in living subjects with abnormal hearts. Am. Heart J. **10:**156-162, 1934.
2. Robb, G. P., and Steinberg, I.: Visualization of the chambers of the heart, the pulmonary circulation, and the great blood vessels in man. Am. J. Roentgenol. **41:**1-17, 1939.
3. Westermark, N.: On bronchostenosis, a roentgenological study. Acta radiol. **19:**285-312, 313-336, 1938.
4. Fleischner, F.: Atelektase und gerichteter Kollaps der Lunge. Fortschr. a. d. Geb. d. Röntgenstrahlen **53:**607-625, 1936.
5. Hampton, A. O., and King, D. S.: The middle lobe of the right lung; its roentgen appearance in health and disease. Am. J. Roentgenol. **35:**721-739, 1936.
6. Hampton, A. O., and Castleman, B.: Correlations of post-mortem chest teleroentgenograms with autopsy findings. Unpublished data presented at the thirty-ninth annual meeting of the American Roentgen Ray Society, Atlantic City, September, 1938. Report of November 30, 1938, meeting of the Suffolk District Medical Society. New Eng. J. Med. **220:**264-266, 1939.
7. Westermark, N.: On the roentgen diagnosis of lung embolism. Acta radiol. **19:**357-372, 1938.
8. Forssell, G.: The rôle of the autonomous movements of the gastrointestinal mucous membrane in digestion. Am. J. Roentgenol. **41:**145-165, 1939.
9. Berg, H. H.: *Röntgenuntersuchungen am Innenrelief des Verdauungskanals.* Second edition. 248 pp. Leipzig: Georg Thieme, 1931.
10. Akerlund, A.: Die Verfeinerung der röntgenologischen Gallensteindiagnostik durch Untersuchung der Sedimentierungs- und Schichtungsverhältnisse in der Gallenblase. Acta radiol. **19:**23-43, 1938.
11. Bernstein, A.: Die Gallenschichtung und das Symptom der horizontal schwimmenden Steinschicht. Fortschr. a. d. Geb. d. Röntgenstrahlen **55:**570-586, 1937.
12. Ettinger, A.: Visualization of minute gallstones (layer formation of bile). Am. J. Roentgenol. **35:**656-661, 1936.
13. Camp, J. D.: Significance of osseous changes in roentgenographic diagnosis of tumors of spinal cord and associated soft tissues. Radiology **22:**295-303, 1934.
14. Hampton, A. O., and Robinson, J. M.: The roentgenographic demonstration of rupture of the intervertebral disc into the spinal canal after the injection of lipiodol, with special reference to unilateral lumbar lesions accompanied by low back pain with "sciatic" radiation. Am. J. Roentgenol. **36:**782-803, 1936.
15. Young, B. R., and Scott, M.: Air myelography: the substitution of air for lipiodol in roentgen visualization of tumors and other structures in the spinal canal. Am. J. Roentgenol. **39:**187-192, 1938.

16. Davidoff, L. M., and Dyke, C. G.: *The Normal Encephalogram*. 224 pp. Philadelphia: Lea & Febiger, 1936.
17. Lysholm, E.; Ebenius, B., and Sahlstedt, H.: Das Ventrikulogramm; Roentgentechnik. Acta radiol. (supp.) **24**:1-75, 1935. Das Ventrikulogramm; die Seitenventrikel. *Ibid.* **25**:1-199, 1937.
Lysholm, E.; Ebenius, B.; Lindblom, K., and Sahlstedt, H.: Das Ventrikulogramm; dritter und vierter Ventrikel. Acta radiol. (supp.) **26**:1-124, 1935.
18. Carty, J. R.: Soft tissue roentgenography: anatomical, technical and pathological considerations. Am. J. Roentgenol. **35**:474-484, 1936.
19. Gratz, C. M.: Air injection of fascial spaces; a new method of soft tissue roentgenography. Am. J. Roentgenol. **35**:750, 1936.
20. Ude, W. H., and Urner, J. A.: Roentgenologic diagnosis of placenta previa. Am. J. Obst. & Gynec. **29**:667-679, 1935.
21. Ude, W. H.; Urner, J. A., and Robbins, O. F.: Roentgenologic diagnosis of placenta previa; indirect placentography. Am. J. Roentgenol. **40**:37-42, 1938.
22. Carvalho, M. A., and McGeary, J. A.: mentioned by Moloy, H. C., and Swenson, P. C.: The use of roentgen ray in obstetrics. Golden's *Diagnostic Roentgenology*. 1935 pp. New York: Thomas Nelson & Sons, 1938. P. 826.
23. Radt, P.: Eine neue Methode zur röntgenologischen Sichtbarmachung von Leber und Milz durch Injektion eines Kontrastmittels (Hepato-Lienographie). Med. Klin. **26**:1888-1891, 1930.
24. Oka, M.: Eine neue Methode zur röntgenologischen Darstellung der Milz (Lienographie). Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:497-501, 1929.
25. Jacobson, L. E., and Rosenbaum, D.: Postmortem findings and radioactivity determinations five years after injection of thorotrast. Radiology **31**:601-607, 1938.
26. Stewart, W. H., and Ghiselin, F. H.: Potential dangers of thorotrast as a contrast agent in roentgen diagnosis; collective review. Internat. Abstr. Surg. **66**:395-397, 1938.
27. Yater, W. M., and Whitmore, E. R.: Histopathologic study of tissues of 65 patients injected with thorium dioxide sol for hepatosplenography, with a follow-up study of 10 old cases. Am. J. M. Sc. **195**:198-205, 1938.
28. Beckermann, F., and Popken, C.: Kontrastdarstellung der Leber und Milz im Roentgenbild mit Jodsolen. Fortschr. a. d. Geb. d. Röntgenstrahlen **58**:519-535, 1938.
29. Stumpf, P.; Weber, H. H., and Weltz, G. A.: *Röntgenkymographische Bewegungslehre innerer Organe*. 516 pp. Leipzig: Georg Thieme, 1936.
30. Hirsch, I. S.: Recording of cardiac movements and sounds by roentgen ray (kymophonoroentgenography). Radiology **22**:403-422, 1934.
31. Scott, W. G., and Moore, S.: Roentgen kymographic studies of aneurysms and mediastinal tumors. Am. J. Roentgenol. **40**:165-172, 1938. Roentgen kymography of respiratory movements of thorax, diaphragm, lungs, bronchi and mediastinal structures. *Ibid.* **37**:721-732, 1937.
Scott, W. G.; Moore, S., and McCordock, H. A.: Roentgen kymographic studies of cardiac conditions. Radiology **28**:196-210, 1937.
32. Kieffer, J.: The laminagraph and its variations; applications and implications of planigraphic principles. Am. J. Roentgenol. **39**:497-513, 1938.
33. Moore, S.: Body section roentgenography with laminagraph. Am. J. Roentgenol. **39**:514-522, 1938.
34. Twining, E. W.: Tomography by means of a simple attachment to Potter-Bucky couch. Brit. J. Radiol. **10**:332-347, 1937.
35. Stewart, W. H.; Hoffman, W. J., and Ghiselin, F. H.: Cinefluorography. Am. J. Roentgenol. **38**:465-469, 1937.
36. Reynolds, R.: Cineradiography by the indirect method. Radiology **31**:177-182, 1938.
37. Janker, R.: Die Leuchtschirmphotographie. Fortschr. a. d. Geb. Röntgenstrahlen **58**:588-593, 1938.
deAbreu, M.: Zwei Jahre kollektiver Roentgenographie. *Ibid.* **58**:574-587, 1938.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 25181

PRESENTATION OF CASE

First Admission. A sixty-four-year-old married colored Bermudian janitor was admitted complaining of inability to void of two days' duration.

For the past year he had noticed increased slowing of the urinary stream. For several months he had had dyspnea on exertion and orthopnea, as well as transient edema of the ankles. During the previous two weeks he had taken digitalis. He had not had precordial pain. There was no history of rheumatism. He had no knowledge of syphilis.

Physical examination showed a well-developed, thin, colored man who was moderately short of breath. Each eye showed a marked arcus senilis but was otherwise negative. The neck veins were not engorged. There was moderate enlargement of the heart to the left. The apical first sound was loud, with a faint, poorly transmitted systolic blow. A_2 was accentuated and tympanitic; P_2 was also loud. A faint diastolic murmur was heard along the left border of the sternum. There were frequent extrasystoles. The blood pressure was 130 systolic, 50 diastolic. Examination of the lungs showed rales at both bases and signs consistent with a moderate amount of fluid in the left pleural cavity. The liver was questionably palpable. There was no edema. The prostate was symmetrically enlarged, being three times normal size.

The temperature was 100.5°F., the pulse 95, and the respirations 48.

Examination of the urine showed a trace of albumin and 30 to 50 red cells and 5 to 10 white cells per high-power field. The blood showed a red-cell count of 3,950,000 with 70 per cent hemoglobin, and a white-cell count of 9600. A blood Hinton test was positive, and the Wassermann test weakly positive. The nonprotein nitrogen of the whole blood was 32 mg. per 100 cc. An electrocardiogram showed slight left-axis deviation, low T_1 and diphasic T_2 and T_3.

An intravenous pyelogram showed prompt excretion of the dye on the right side, slight delay on the left. The kidney pelves were negative. There was evidence of Paget's disease in both ilia and in the second lumbar vertebra. X-ray films of the chest showed the heart enlarged in the region of the left ventricle. There was increased density in the left lower and middle lung fields. The right costophrenic angle was clear. A lateral view showed that the area of increased density lay posteriorly, having a well-defined anterior convexity. There was a localized area of decreased density in the anterior mediastinum just above the diaphragm, with a well-defined border of slightly increased density. The intercostal spaces on the left side were narrowed, and there was some periosteal new-bone formation about several ribs.

On the third hospital day a bilateral vasectomy was done. The patient was taught to catheterize himself, given digitalis and sent home on the twenty-first hospital day. He was to return for prostatectomy after improvement of his general condition.

Final Admission (three months later). He complained of severe dyspnea and orthopnea of six days' duration, without chest pain. Four and a half grains of digitalis daily had been continued. Three days before re-entry he vomited once.

Physical examination showed the patient in marked respiratory distress, with Cheyne-Stokes respiration. The pupils were large and reacted well. The neck veins were full. The tongue was cyanotic. Examination of the heart was essentially the same as on the previous examination. The blood pressure was 130 systolic, 60 diastolic. The lungs showed rales at both bases, with evidence of a moderate amount of fluid at the right base. The liver edge was not palpable. There was no edema.

The temperature was 98.6°F., the pulse 140, and the respirations 25.

The urine showed a slight trace of albumin. The blood showed a red-cell count of 4,700,000 with 86 per cent hemoglobin, and a white-cell count of 16,100 with 92 per cent polymorphonuclears. The serum nonprotein nitrogen was 45 mg. per 100 cc. A blood Hinton test was positive, a Wassermann test weakly positive.

The patient was kept in a cardiac bed and given oxygen and carbon dioxide without improvement. An electrocardiogram on the second hospital day showed a variable P-R interval due to ventricular escape. The ventricular rate was 90. T_1 and T_2 were inverted, T_3 diphasic, and T_4 showed late inversion. On the third hospital day the patient was semicomatose and did not respond to various stimulants. The respirations were 32, the temperature 98°F., and the pulse 95. The blood pressure had risen slightly. On the following day there was no change, but on the fourth day the patient rapidly became worse, the respirations ris-

ing to 50, the pulse to 150 and the temperature to 103°F. An electrocardiogram at this time showed an auricular rate of 105 and a ventricular rate of 140. T_1, T_2 and T_4 were inverted. There were nodal tachycardia and nearly complete A-V dissociation. The patient rapidly failed and died a few hours later, on the fourth hospital day.

Differential Diagnosis

Dr. Howard B. Sprague: I am prepared to modify whatever views I may have about the final episode in this case in accordance with what Dr. Hampton may be able to tell me about the x-ray films.

On the first admission we have an arteriosclerotic Negro, with positive Hinton and Wassermann tests, who came in with an obstructing prostate. There is no evidence to show that this was a cancer of the prostate, but there may have been some neoplastic disease in it. Our attention here is focussed on the heart and lungs and the renal situation. So far as the heart is concerned we have left ventricular enlargement, an aortic diastolic murmur, a degree of aortic regurgitation which can be measured by the arterial pulse and the low diastolic level, an aortic second sound which is accentuated and tympanitic, and an increase in the pulmonary second sound, all of which indicate left ventricular failure and pulmonary hypertension. The first sound was loud instead of diminished, which is rather unusual. So far as etiology is concerned, there does not seem to be adequate reason to suspect hypertensive or rheumatic heart disease. At his age and in the face of the positive blood it would take a good deal of courage to avoid a statistical bias and say this man did not have aortic syphilis. I assume that he had.

He showed signs consistent with fluid in the left pleural cavity. I am not quite clear about this part of the history. Later on we hear that he came back and showed rales at both bases, with evidence of a moderate amount of fluid at the right base. I do not know whether it means in addition to the signs at the left base or that the signs at the left base had, in the meantime, cleared up. If this were an effusion in the left base that cleared up under digitalis and recurred on the right, we might have a different point of view. His renal situation at the time of the first entry was impressively poor. The nonprotein nitrogen was 32 mg. per 100 cc., and toward the end it was 45 mg. He showed only a little albumin in the urine. He was sent home at that time on digitalis and for three months kept it up on a ration of 4½ gr. a day, which is a good-sized dose and may be responsible for the final disturbance of cardiac rhythm. He had evidence of digitalis toxicity. We have only one x-ray examination and I should like to have Dr. Hampton talk about that. It was taken at the first admission.

Dr. Aubrey O. Hampton: We have two films. The second was taken primarily for obtaining a lateral view of the chest. There is a large heart, apparently due to left ventricular hypertrophy. The supracardiac shadow is widened without evidence of aneurysm, but the usual curve of the aortic knob is gone. The aorta is dilated in the ascending portion, not enough to make a positive diagnosis of aneurysm or to rule out the possibility of its being due to hypertension.

This process at the left base is quite interesting in view of the fact that it was completely ignored by the surgeons. The X-ray Department was upset about that. We thought it was obvious evidence of longstanding infection in the pleura; in the lateral view, it is quite sharply defined and in all respects corresponds to an encapsulated empyema. Dr. Edward D. Churchill has pointed out that the ribs in the region of chronic inflammatory disease in the pleura are definitely thickened, and the rib changes in this case make us more certain that the shadow is due to infection. We thought at first that this periosteal thickening always meant pus, but it does not. It can occur with longstanding pleural effusion without pus. So we cannot insist that in this case there is pus in the pleural cavity, but we can be sure that the disease is inflammatory and that the lesion is sharply localized and has the appearance of encapsulated fluid. We also saw this sharply defined area of rarefaction, seen only in the lateral view, at the anterior margin of the lung, which looks like a bleb. Although there is no other evidence of gross emphysema in the chest and although we could interpret this as a pulmonary cyst, the latter are rare and the lesion is probably an emphysematous bleb.

Dr. Sprague: What is your reaction to the statement about the ribs' being close together?

Dr. Hampton: That means there is retraction on the left side of the chest due to longstanding pleurisy. There is no question that this man had had an infectious process in the pleura for a long time.

Dr. Sprague: What about the problem of pulmonary collapse on that side?

Dr. Hampton: There is no evidence of collapse of the lung except this area of density, which can be explained by the shadow in the pleura.

Dr. Sprague: Do you think this is all outside the lung?

Dr. Hampton: Yes.

DR. SPRAGUE: Could you say anything about the aorta in the lateral view?

DR. HAMPTON: I think it is diffusely dilated. I do not see any aneurysm.

DR. SPRAGUE: There would seem to be a definite increase in the first portion of the arch.

DR. HAMPTON: It is dilated.

DR. SPRAGUE: One might assume, on hearing the discussion, that these findings were present before and after he came back. What was found at the right base was in addition to what he had had at the left base, and was no doubt due to congestive failure. This left basal lesion with its relation to the diagnosis of syphilis is the bothersome thing.

At the time of his final entry there was very severe dyspnea and orthopnea without pain and signs of increasing congestive failure, with a febrile episode at the end which was probably due to a pneumonic process. I am trying to hook this up into one diagnosis, that of a syphilitic process.

You do not see anything in this chest film that makes you think he had any metastatic lesion from the prostate?

DR. HAMPTON: No.

DR. SPRAGUE: The other findings at the end of his illness are of no help in making a diagnosis.

He was an arteriosclerotic individual who was very ill and who probably had a diffuse syphilitic aortitis. From what evidence we have, it is not possible to say he had an aneurysm of the descending aorta with pulmonary collapse. He may have had some aneurysmal dilatation of the arch or even of the intrapericardial portion of the aorta, and the story certainly suggests progressive narrowing of the coronary ostia. I am unable to connect the signs at the left base with the underlying condition but am unwilling to guess at anything other than a syphilitic process in the pleura. The final cardiac episode with this type of arrhythmia and dissociation can well be explained by the large doses of digitalis.

DR. F. DENNETTE ADAMS: How often do you see a syphilitic patient die of congestive failure with no more evidence of valvular damage than this man showed?

DR. SPRAGUE: I have to invoke involvement and narrowing of the coronary ostia. With such lesions, syphilitic patients may die with severe dyspnea and congestive failure and without a great deal of peripheral edema.

DR. CHAMP LYONS: These blebs are not numerous enough to assume that emphysema precipitated cardiac failure?

DR. SPRAGUE: One would think in such a case that there would be some evidence of right-sided strain, such as cor pulmonale, rather than left-sided cardiac hypertrophy.

DR. LYONS: Could not prolonged toxemia from suppuration in so old a man be responsible for myocardial failure?

DR. PAUL D. WHITE: He did have fever on the first admission and leukocytosis on the second.

DR. SPRAGUE: The temperature was only 100.5°F., and he came in with an obstructing prostate.

Do you believe, Dr. White, that we can say that toxemia from infection induces heart failure?

DR. WHITE: It may if the heart is already diseased. Moreover, this man was old enough to have arteriosclerotic coronary changes, besides the syphilitic aortitis affecting the mouths of the coronaries.

DR. SPRAGUE: The electrocardiogram is consistent with a digitalis effect. We know he had arcus senilis, but that is all in the way of sclerotic change.

DR. WHITE: Probably the arrhythmia was not directly responsible for death, although in combination with other factors it may have played something of a role. The last straw was doubtless the pulmonary complication on top of coronary insufficiency, which in turn was largely of syphilitic origin.

CLINICAL DIAGNOSES

Syphilitic heart disease with aortic regurgitation.
Syphilitic aortitis.
Generalized and cerebral arteriosclerosis.
Benign prostatic hypertrophy.

DR. SPRAGUE'S DIAGNOSES

Syphilitic aortitis with aortic regurgitation.
Chronic syphilitic lesion of the left pleura?
Arteriosclerosis.
Obstructing prostate (benign).
Digitalis intoxication.
Terminal bronchopneumonia.

ANATOMICAL DIAGNOSES

Syphilitic aortitis with aortic valve involvement.
Hypertrophy and dilatation of the heart.
Gumma of left pleural cavity.
Thrombosis of right auricle and periprostatic and popliteal veins.
Infarcts of lung, multiple.
Benign hypertrophy of prostate.
Cystitis, chronic.
Pyelonephritis, chronic.
Arteriosclerosis.

Pathological Discussion

Dr. Tracy B. Mallory: The postmortem revealed very obvious syphilitic heart disease. The aorta showed rather diffuse dilatation, with numerous scattered stellate scars. The coronary mouths appeared to be nearly 1 cm. above the aortic cusps, a finding indicating that the cusps had been drawn down and retracted, as is so common in syphilis. They were not, however, separated as they often are, so that the degree of regurgitation was, I think, a mild one. The mouth of the right coronary was quite markedly narrowed by scar tissue. It showed a few atheromatous plaques but no further narrowing, and the left coronary was free. The heart was moderately hypertrophied. The interesting finding in the autopsy was a large lesion at the base of the left pleural cavity (Fig. 1). It consisted of a roughly pyramidal mass of fibrous tissue measuring 7 by 5 by 4 cm. It was firmly attached to the lower four thoracic vertebrae and the corresponding ribs but did not penetrate the periosteum and involve the bones. On its medial aspect it was adherent to the aorta, but a plane of cleavage could easily be developed. It was adherent to, but easily separable from, the lung. On section many irregular, yellowish necrotic areas were found scattered through the fibrous tissue. There were no purulent foci, no cavities and no areas of solid calcification, although the tissue seemed slightly gritty on section.

Figure 1. *Posterior View of the Thoracic Organs.*

To the left of the aorta is the transected wedge-shaped gummatous mass which occupied the lower portion of the left pleural cavity.

The problem centers around what this mass is. The gross appearance is perfectly consistent with that of a gumma, but the location is an unusual one. Stains for spirochetes are negative. The histology does not in the least suggest tuberculosis. It is possible for an undrained empyema to organize and leave a scar which might be something like this. On the other hand, my personal hunch is that the lesion is probably gumma. I do not know of any way to prove it with certainty.

A Physician: Are not the empyemas which organized more apt to show calcium?

Dr. Mallory: Yes; I should expect more calcium. There was some, but just occasional small gritty particles.

He had, of course, an enlarged prostate and the usual sequelae of that — cystitis, dilated ureters, dilated kidney pelves on both sides and generalized infection of the urinary tract. The terminal episode in this case was one of pulmonary embolism. He had multiple infarcts throughout both lungs, and there was a choice of numerous sources from which the emboli might have come. There were thrombi in the right auricle and in both popliteal veins and many in the periprostatic plexus, one of which I think probably was the source.

Dr. Sprague: Do you think we always ought to say pulmonary embolism? I have got tired of saying it in every case, and with this temperature reaction I thought I should take a chance and say pneumonia.

Dr. Mallory: In saying pulmonary embolus rather than terminal pneumonia I think one is statistically more apt to be right.

CASE 25182

Presentation of Case

A fifty-seven-year-old married commercial agent was admitted complaining of intermittent incontinence, numbness in the extremities and abdominal distention.

At the age of twenty-one years the patient had had gonorrhea and a venereal wart on the prepuce which was "burned" and healed in about two weeks. A urethral stricture developed which was dilated with sounds and apparently cured in about six months. No blood test was done, and he remembered no skin eruption. Until seven years before entry he was well and healthy, and at this time his wife noted that he hesitated in his speech.

This apparently did not progress significantly. One and a half years before admission intermittent enuresis developed, but there was no incontinence during the day. Three months before entry this condition became considerably worse and he visited a physician who found "positive serology." Intravenous injections were begun at this time. Three days before admission he noted numbness in both lower extremities, muscle twitchings and beginning ataxia, worse on the right side. He had occasional severe tonic contractions of the calf and thigh muscles, but no pain. During the previous twenty-four hours there was oliguria, and distention of the lower abdomen. He had had no rectal incontinence but recently had noted increasing constipation.

Physical examination showed a moderately obese male in no acute discomfort. The pupils were very small and did not react to light. The mouth was said to be asymmetrical, but there was no noticeable muscular weakness and no further details were recorded. Examination of the heart and lungs was not remarkable. The blood pressure was 140 systolic, 80 diastolic. The abdomen showed generalized distention. The bladder was distended. Rectal examination showed normal sphincter tone. The Romberg test was positive. There was moderate ataxia. Pain and temperature sensations were diminished over both lower extremities. There was almost complete absence of vibratory sense. The abdominal reflexes were absent except in the left hypochondrium. Babinski signs were positive bilaterally. The finger-to-nose and heel-to-shin tests were poor.

The temperature was 98.2°F., the pulse 82, and the respirations 22.

The urine examination was negative. The blood showed a red-cell count of 4,780,000 with 85 per cent hemoglobin, and a white-cell count of 8800 with 71 per cent polymorphonuclears. A blood Hinton test was positive. A blood smear showed malarial parasites. A lumbar puncture showed an initial pressure of 150 mm. of water and normal dynamics. The spinal fluid showed 2 lymphocytes per cubic millimeter and a total protein of 67 mg. per 100 cc. A goldsol curve was 5555532100. A spinal-fluid Wassermann test was strongly positive.

On the second day after entry the patient was inoculated with malarial organisms. During the first week in the hospital the patient's abdominal distention increased and there was increasing discomfort. Examination showed generalized abdominal distention, and the cecum was thought to be especially dilated. There was no tenderness, spasm or audible peristalsis. An x-ray of the abdomen at this time showed that the right half of the colon was filled with gas and markedly dilated. The cecum was huge. The small intestine also contained gas and was dilated. On the following day the abdominal pain had increased in severity and the patient vomited foul-smelling material several times. Distention became more marked, the pulse rose to 110, and the patient perspired freely. The temperature, which had not been above 99°F. during the preceding eight days, rose to 100°F. Shortly thereafter a laparotomy was performed.

He died on the second postoperative day, and during the last two days his respirations rose from 20 to 35.

Differential Diagnosis

Dr. Oliver Cope: I should like to discuss the differential diagnosis before we turn to the x-ray films, because I suspect that the latter may be helpful in making the diagnosis.

Dr. Tracy B. Mallory: The films have been lost, so you need not be afraid of their giving away the diagnosis.

Dr. Cope: Then I should like to recall an incident which occurred during the study of another patient seen here recently. This patient had the disease from which I suspect the patient under discussion suffered. The surgeons, among them myself, and members of the X-ray Department were struggling to make a diagnosis. The x-ray films were spread out on the illuminator. At this moment Dr. Holmes walked by, glanced at them casually and said, "H'm, neurosyphilis, I see," and passed on into his office. That is why I thought it would be better to wait until after my discussion before we allowed Dr. Holmes to look at the films.

I think the diagnosis lies between a "cord colon" and true mechanical obstruction of the large bowel. It is obvious that the man had neurosyphilis and, with it, involvement of the spinal cord. Whether the recent malarial therapy had anything to do with the symptoms when he entered the hospital and those for which he was operated on, it is difficult to tell. It is certain from the history that he had a distended "cord bladder," with enuresis. The disease had recently been progressive, and it is significant that the first intestinal symptoms appeared when the bladder symptoms were becoming more pronounced.

I am not going to try to discuss the various lesions in the colon which, through production of mechanical obstruction, might enter into the differential diagnosis. I want to weigh mechanical obstruction, on the one hand, against the type of dilated colon seen in central-nervous-system syphilis, on the other. In favor of paresis or central-nervous-system syphilis as the origin of

the symptoms in this patient is the fact that we know this disease was already present and that it had already produced a cord bladder. Whether the recent exacerbation of bladder symptoms, together with the onset of symptoms from dilatation of the colon, was due to spreading disease in the cord from malarial treatment, I cannot tell, and I am not competent to discuss it. Also in favor of the tabetic colon is the observation that the first abdominal distention occurred without any symptoms other than constipation. It is true that he had some discomfort later on, but this he might have had from abdominal distention rather than from intestinal dilatation. If there had been a primary mechanical obstruction I should have expected intermittent pain. Of course the lack of sensation may have been due to injury in the cord, since we know that there was loss of sensation in the extremities. In other words he might have had true mechanical obstruction, and pain was absent because of the nerve lesion. The examination of the abdomen is also in favor of the diagnosis of cord colon. The absence of audible peristalsis, of tenderness and of spasm is noted, and we should expect one or all these findings with this degree of dilatation had it been due to pure mechanical obstruction. In the cord colon, peristalsis is not audible because feces in the cecum and right colon are usually semi-solid and there is not the swish and rush of fluid content encountered in mechanical obstruction.

The diagnosis of cord colon does not necessarily explain the fecal vomiting which the patient had terminally, and also does not take into account, so far as my own experience is concerned, the dilatation of the small bowel. I do not know, however, why dilatation of the small bowel cannot occur just as well as dilatation of the large intestine, since the nerve lesions which lead to dilatation of the latter would also be present in the levels involving the former. The fecal vomiting is not explained unless we assume the obstruction had come to such a point that there was an actual backing up of contents of the small intestine into the stomach. In other words, the nerve lesion and consequent functional disability had resulted in a virtual mechanical obstruction due to fecal impaction, and the fecal vomiting was secondary to that. It is my inclination to put the picture together in that way.

As to the final contributing cause of death, we are not told what the operation was. From the record as given the only thing we have as a clue is the rise in respirations to 35. That could have been due, of course, to a postoperative pulmonary complication, or to encroachment on the vital capacity in the chest due to increasing abdominal distention. Another possibility, which undoubtedly entered to some extent into the immediate cause of death, was the electrolyte imbalance subsequent to the intestinal obstruction and vomiting. A third possibility is peritonitis subsequent to operation, and increasing distention.

In conclusion, I am therefore forced to make a diagnosis of syphilitic paresis with cord paralysis, a cord bladder and a cord colon, if I may coin the expression. With extensive dilatation of the colon there occurred electrolyte loss from vomiting, and possibly pneumonia and peritonitis, as contributing causes of death.

Dr. Mallory: The operation was simply a cecostomy.

Dr. Cope: That would not change my diagnosis.

Dr. Harry C. Solomon: I think the first thing to comment on is the correct and very clever diagnosis as regards the colon. I might add that it is very uncommon to get a tremendously bloated colon of this sort in any of the syphilitic diseases of the spinal cord.

There are one or two omissions in the history. This man, when I first saw him, had been under the care of a physician who had treated him for two or three months prior to his coming to this hospital. Just prior to admission he had had a sudden onset of what was said to be ataxia. He became suddenly incapable of walking, and within twenty-four hours he was admitted. Before this he had been receiving tryparsamide, and the question arose whether there was any relation between the drug and the sudden collapse of the lower extremities, whether treatment had caused a Herxheimer reaction or some degeneration of the spinal cord. He was given malarial treatment on his arrival.

I take a good deal of exception to the diagnosis of general paresis. Clinically this man showed no symptoms of cerebral involvement. Before a diagnosis of general paresis, which is by ordinary definition a psychosis, is definitely established, there has to be evidence of mental changes. This man had a positive goldsol curve which is common enough in cord disorders as well as characteristic of general paresis. Our examination, aside from the pupils, which so commonly show abnormalities in cord syphilis, showed no evidence of lesions in the cerebrum, and the problem seemed to be merely that of a cord lesion. He had something that suggested a transverse lesion. Furthermore, he had symptoms characteristic of disorders of the lateral and posterior columns — a loss of vibratory sense and urinary difficulty.

It was after malarial treatment had been started that his colon began to blow up quite progressively and fairly rapidly. Stupes, enemas, rectal tubes and the like had no effect on the situation. There-

fore Dr. E. Parker Hayden was asked to come in and see him as regards operative procedure. The x-ray films, as indicated, were very characteristic of an ileus, just dilated bowel without any evidence of obstruction. Dr. Hayden opened the colon and drew off a good deal of gas, a procedure which gave the patient quite a bit of temporary relief. He immediately began to blow up again in the same fashion, and he succumbed to what seemed to be a bronchopneumonia.

Dr. George W. Holmes: This patient had only one film taken and that showed the gas-distended colon. The films which I am putting up now come from another very similar case, the one to which Dr. Cope referred at the beginning of his discussion. The first thing that one notices is the prominent aorta. That would naturally lead you to suspect that the patient had syphilis but is not enough to make that diagnosis. It is a well-known fact that in a certain number of patients with neurosyphilis we do get a relaxed and dilated colon. Dr. James R. Lingley examined a number of cases at the McLean Hospital and found in a high percentage an enormously dilated colon. Of course the appearance in this film could be due to obstruction, but at the time I saw it, an enema had been given and we knew there was no obstruction in the colon. This emphasizes the danger, in cases of dilated large bowel, of accepting a diagnosis made from plain films alone. The surgeons have objected to our giving a barium enema in this type of case, and I think they are justified, because it interferes with the operation; but unless we do it we can never be certain whether there is obstruction or only a relaxed dilated bowel. The points, then, of interest in this case are: first, the dilated colon which was proved by barium enema not to be due to obstruction; and second, the prominence of the aorta.

Dr. Solomon: The malarial treatment was given as a last desperate attempt; in the case of the sudden onset of symptoms suggesting transverse myelitis, such as this man showed, one has no assurance that anything else is going to give relief.

Clinical Diagnoses

Central-nervous-system syphilis.
Paralytic ileus.
Bronchopneumonia.

Dr. Cope's Diagnoses

Central-nervous-system syphilis.
Cord colon.
Cord bladder.

Anatomical Diagnoses

Central-nervous-system syphilis, meningovascular type.
Myelitis.

Pathological Discussion

Dr. Mallory: At operation an enormously distended cecum was found. It was so large it was almost impossible to manipulate. It was necessary to put in a needle and withdraw a considerable amount of gas before a cecostomy could be done. That drained the gas from a limited portion of the ascending colon but not from the distended descending colon on the left side. He proceeded downhill with renewed and progressive dilatation of the intestines. At the time of autopsy the entire small bowel was markedly dilated and the large bowel looked as if it had never been decompressed. The rest of the autopsy showed nothing that could be considered as the cause of death. The lungs showed diffuse collapse, undoubtedly due to the high diaphragm, and marked congestion and edema, which might be interpreted as evidence of shock. There was no significant amount of pneumonia. The examination of the spinal cord did show a localized lesion in the thoracic portion. I shall ask Dr. Kubik to describe it.

Dr. Charles S. Kubik: The arachnoid of the entire thoracic cord was pearly gray in color, and opaque. There were fibrinous adhesions in the subarachnoid space, and the cord in the mid-thoracic region was softer than normal. A careful search did not reveal evidence of thrombosis in any of the visible spinal arteries. Microscopic sections of the spinal cord, brain stem and brain showed a slight to moderate lymphocytic exudate, perivascular infiltration with lymphocytes and plasma cells, and varying degrees of endarteritis. There was a thinning out of nerve fibers along the periphery of the cord. In the upper third of the thoracic cord on the right side was a large focus of degeneration involving the posterior half of the lateral column and extending a short distance into the posterior column. The degeneration was not complete. Although the myelin was completely destroyed, many of the axis cylinders were preserved. This had the appearance of a vascular lesion and was unquestionably responsible for the myelitic symptoms.

The case provides a fairly good example of meningovascular neurosyphilis.

Dr. John D. Stewart: The stomach was not dilated?

Dr. Mallory: Not particularly.

Dr. J. H. Means: I should like to ask if any attempts were made to deflate him by Dr. Jacob Fine's method of oxygen inhalation.

Dr. Mallory: That apparently was not tried, nor was spinal anesthesia.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
The New Hampshire Medical Society
The Vermont State Medical Society

Editorial Board

George G. Smith, M.D. — Dwight O'Hara, M.D.
Joseph Garland, M.D. — John P. Sutherland, M.D.
William B. Breed, M.D. — Stephen Rushmore, M.D.
George R. Minot, M.D. — Hans Zinsser, M.D.
Frank H. Lahey, M.D. — Henry R. Viets, M.D.
Shields Warren, M.D. — Robert M. Green, M.D.
George L. Tobey, Jr., M.D. — Charles C. Lund, M.D.
C. Guy Lane, M.D. — John F. Fulton, M.D.
William A. Rogers, M.D. — A. Warren Stearns, M.D.

Associate Editors

Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.
Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Saturday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the New England Journal of Medicine, 8 Fenway, Boston, Mass.

INDUSTRIAL MEDICINE

Whenever the adequacy of medical care in any field is under discussion the attention of the profession is directed to the problems involved. If sociologic, public-health and economic questions are included in the program the appeal for consideration has especial merit. Industrial medicine includes all these three subjects, and imposes on the doctor practicing under the provisions of any workmen's compensation act a range of responsibilities which were brought to the attention of the first annual Congress on Industrial Health held in Chicago, January 9. There were in attendance more than two hundred prominent industrial medical practitioners and representatives of insurance and industry.

Massachusetts, which has been given a prominent position among her sister states because of her striking contributions to the welfare of all classes, passed a law, which became effective in 1912, providing for workmen's compensation. Only two states — Arkansas and Mississippi — have failed to enact workmen's compensation laws, and the legislature of the former is now considering a bill related thereto. The act in Massachusetts has been amended from time to time and now protects the injured workman, his employee and the insurance company, so far as possible with justice to each interest. The provisions of this statute cover, besides surgical care and operations, medical conditions to which the workman may be liable, such as sunstroke, hernia, heart trouble, tuberculosis, pneumonia, incapacity caused by exposure to granite dust and other situations in which it can be shown that the employer may not have exercised due care in protecting the employee from deleterious influences.

Both the insurance companies and employers are co-operating in eliminating conditions in industrial plants which are inimical to the well-being of the workers, but even so the administration of the statutes is a complicated procedure involving repeated hearings and, not infrequently, resort to reviews by superior and supreme courts. Hence, in so far as the doctor is brought into a case his responsibilities extend beyond the care of the patient.

Insurance companies have given generous commendation of the medical work done by physicians in connection with service to injured workmen, but have stated that the quality is highest in the cities and large towns.

This led one of the speakers* before the Congress to point out that medical schools do not or cannot properly prepare students to fill the present requirements involved in the practice of industrial medicine, with the result that doctors in small communities may be quite deficient in experience and training, in the first instance, to meet the exacting conditions often encountered in dealing with the patient and, later, to keep records and to construct reports that help the industrial-accident-

*Mr. Ambrose B. Kelly, of the American Mutual Alliance, Chicago.

board members or even the courts in arriving at just decisions. In this field, as it is sometimes in general practice, the first visit to and the eventual treatment of a patient may determine success or failure in dealing with a given case.

With these underlying premises the contention of this speaker that medical societies should include industrial medicine in their programs for post-graduate instruction is sound. He stated that for the physician's protection as well as that of the patient the inexperienced doctor should prepare himself for dealing with cases coming under the operation of the workmen's compensation acts or refrain from carrying on this practice. Anyone may have to respond in an emergency and render first aid, but properly qualified surgeons are rarely more than thirty minutes away from a given locality in Massachusetts and should be called. The Workmen's Compensation Act is a contribution to the welfare of those working people who come within the scope of the provisions defined in the act, and should have the support of the medical profession.

The Council of the Massachusetts Medical Society at its last meeting voted that the President appoint a committee to study the problems of industrial health. If this committee should recommend inclusion of a broad public-health educational program in the postgraduate instruction courses now in operation, it might well include some of the phases of the service now carried on under the Workmen's Compensation Act.

DRINKING AND TRAFFIC ACCIDENTS

The toll of traffic accidents has forced upon us the problem of the "accident-repeater" and also that of the driver under the influence of alcohol. The last report[1] of the Committee on Tests for Intoxication, made to the National Safety Council, brings out two important points: half the drivers killed in automobile accidents had been drinking and one third the pedestrians killed had been drinking.

The effect of alcohol in impairing judgment and mechanical ability is too well known to need comment. The report states that the average driver with a blood-alcohol concentration of 0.15 per cent or more is fifty-five times as liable to have a personal-injury accident as is one without alcohol. While there are minor variations in the response of different persons to alcohol, in general the commonly accepted evidences of intoxication have paralleled the alcohol concentrations in the blood and tissues.

In Evanston, Illinois, a study by Holcomb[2] showed that 12 per cent of 1750 non-accident drivers stopped and tested had been drinking, whereas 47 per cent of the accident drivers had been drinking. He also found that from midnight to six in the morning was the most dangerous period on the road from the standpoint of drunken driving, inasmuch as over 40 per cent of all drivers tested during that period had been drinking.

After thorough tests of various procedures for examining drivers involved in accidents for evidence of alcohol, the committee advises the use of special report forms, chemical tests for the presence of alcohol in breath, blood or urine, and medical examination to prevent the confusion of illness or injury with alcoholism. Only by the accurate determination of the degree of alcoholism and by the prompt and sure punishment of the drinking driver can this menace be curbed.

REFERENCES

1. Report of Committee on Tests for Intoxication. National Safety Council: Chicago, 1938.
2. Holcomb, R. L.: Alcohol in relation to traffic accidents. J. A. M. A. 111:1076-1085, 1938.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

Bleeding in the Puerperium

Mrs. M. G., a twenty-five-year-old primipara, at term, was admitted to the hospital at 8 a. m. on September 17, 1932 in mild labor. The membranes had ruptured.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

The family history was irrelevant. The patient had had no childhood diseases, but she had undergone an appendectomy at nine years of age. Catamenia began at twelve, were regular with a twenty-eight-day cycle and lasted four days. Her last period was December 10, 1931, making her due for delivery September 17. The prenatal period had been entirely normal.

Examination one hour after admission showed the head well engaged in the LOA position; there was no dilatation of the cervix. Contractions were occurring at six- to eight-minute intervals.

Under Sodium Amytal analgesia the patient progressed slowly to full dilatation at 3:30 a. m. the following morning. Under nitrous oxide and oxygen anesthesia an 8 lb., 5 oz., baby was delivered by low forceps at 4:30 a. m. There was a small vestibular tear, in which two stitches were placed, but no perineal laceration. The placenta separated in fifteen minutes and was expressed by the method of Credé. As the placenta was being delivered, the patient came out of anesthesia and moved violently, resulting in some tearing of the placenta as it was removed from the vagina. The placenta was pieced together after delivery and appeared to be complete. As there was no abnormal bleeding and the fundus contracted well, exploration of the interior of the uterus seemed contraindicated.

The temperature remained normal until the evening of the third day when it rose to 101°F.; the pads were slightly foul, and there was some tenderness in the left lower abdomen. The temperature remained elevated for three days, reaching a maximum of 102°F., then dropped to normal on the morning of the eighth day and remained normal until the evening of the tenth day. The lochia during this time had a foul odor but was serous in character. Treatment had been limited to ice applied to the lower abdomen and elevation of the head of the bed. On the evening of the tenth day the patient passed two large blood clots, and almost simultaneously the temperature rose to 103°F. One half drachm of fluid extract of ergot, every four hours, was prescribed. The patient continued to flow freely but not alarmingly. The temperature remained between 103 and 104.5°F., and the pulse rose gradually to 120 but was of good quality. One cubic centimeter of posterior pituitary extract was given hypodermically every four hours. On the eleventh day the patient had a severe chill. On the morning of the twelfth day the bleeding had become alarming in amount and the pulse had risen to 130 and had become definitely weaker. The temperature was 104.5°F. The white-blood-cell count was 10,350, and the red-blood-cell count 2,420,000. A differential count showed 75 per cent polymorphonuclears, 13 per cent lymphocytes, 4 per cent large mononuclears and 8 per cent miscellaneous cells. It was evident that active intervention must be taken despite the temperature.

Under light nitrous oxide and oxygen anesthesia the uterus was quickly but lightly curetted, and a moderate-sized piece of placental tissue and some additional debris were removed. The uterus was swabbed with 7 per cent tincture of iodine and tightly packed with sterile gauze. Two cubic centimeters of posterior pituitary extract was given intramuscularly, followed by 1 cc. every four hours. Ice to the fundus was continued. Due partly to lack of co-operation on the part of the patient's family, a satisfactory transfusion donor could not be obtained.

In spite of the measures taken, the patient continued to ooze through the pack. Five cubic centimeters of hemostatic serum (La Penta) was given intramuscularly. The flow then diminished and gradually became brownish in color but still had a foul odor. The pack was removed forty-eight hours after the curettage, without further bleeding. The temperature continued to range from 98.4°F. in the morning to 103 or 104°F. in the afternoon. The vaginal discharge was scanty and serous in appearance, with a foul odor. Nonspecific protein therapy in the form of 10 cc. of sterile milk intramuscularly daily for five doses was tried with no effect on the temperature. The patient developed an abscess over the right deltoid muscle, probably resulting from an infected hypodermic-needle puncture, which was opened on the twenty-second day with no effect on the temperature. Repeated pelvic examinations were negative, as were blood cultures. About the twenty-third postpartum day a slight but progressive drop in both morning and evening temperatures began without additional therapy, and on the twenty-sixth day a sudden drop to normal occurred. The temperature thereafter remained normal, and the patient was discharged on the thirty-seventh postpartum day.

Comment. It is always difficult, no matter how carefully a placenta is examined, to be certain that it is intact. So often it appears ragged as though a piece were lacking that, unless bleeding occurs after the birth of the placenta, only rarely does one think of entering the uterus because of a piece that may be retained. Furthermore, such pieces of placenta are often spontaneously extruded without any accompanying hemorrhage.

The temperature which this patient ran after the third day of her convalescence was undoubtedly due to a saprophytic infection. The treatment

of these cases when not associated with hemorrhage is always conservative. Ice to the fundus, a modified Fowler's position and oxytocics are almost always sufficient. When this patient began to bleed on the twelfth day, it was evident, in spite of her temperature, that the uterus contained retained tissue. Hemorrhage is the only indication for entering the uterus after delivery, and this is true even in the presence of sepsis. The more conservatively the uterus is explored the better it is for the patient. The pieces may often be removed with the fingers or by ovum forceps, but if a curet must be used, it should not be a sharp one and the operation cannot be done too delicately. It is surprising how little placental material may be obtained; it takes but a small piece to cause very free bleeding. Packing of the uterus after it has been explored in the presence of bleeding is an essential part of the performance. This pack is used to control further immediate bleeding and also acts as an irritant whereby other fragments of placenta may be loosened.

The use of LaPenta hemostatic serum, while apparently of value in this case, is not in general use. Transfusion at the time when the red count was 2,420,000 would certainly have been valuable.

While the placenta which caused this bleeding may have abetted the infection, it was not per se the cause of the infection. Cultures of the lochia might have been valuable for the establishment of specific treatment.

It should be borne in mind that every case, whether septic or not, which bleeds profusely after the first few hours after delivery is always associated with an intrauterine lesion. This may be a placental polyp or a true accreta; most frequently it is a piece of retained placenta. The symptom demands intrauterine exploration and, oftentimes, transfusion.

LEGISLATIVE NOTES

Below is listed the progress in the Legislature of some of the bills in which the Massachusetts Medical Society is interested.

Favor

S. 258. Bill relative to the meaning of the terms "rendering medical service," "practice of medicine" and "holding oneself out as a practitioner of medicine" and to exempt dentists, optometrists and chiropodists in certain cases from penalties provided for the unlawful practice of medicine. The bill was proposed by the Board of Registration in Medicine. It is favored by the Society with the addition of the following sentence at the end of Section 5A: "Such treatment shall include examination of any secretion, excretion or discharge of the living body."

This bill has been given leave to withdraw.

H. 59. Identical with S. 258.

This bill has been given leave to withdraw.

H. 60. Bill requiring annual licensing of qualified physicians.

With certain changes this bill has been favorably reported by the Committee on Public Health and given to the Committee on Ways and Means.

H. 72. Bill providing for the care of certain infants prematurely born. It was proposed by the Department of Public Health, and corrects defects in the previous bill.

This bill was amended to H. 2080 and has been passed to be engrossed.

H. 73. Bill providing for supplementary reporting of congenital deformities and birth injuries in infants. The bill was proposed by the Department of Public Health and requires that supplementary reports be sent to this department.

It has been passed to be engrossed.

H. 74. Bill requiring the clerk or registrar in each city or town to give to persons who file notice of intention of marriage suitable information concerning gonorrhea and syphilis. The bill was proposed by the Department of Public Health and it contains no compulsion.

A report of no legislation necessary has been accepted in the House.

H. 75. Bill making various changes in the laws relating to foods and drugs. The bill was proposed by the Department of Public Health in order to bring the state law into line with the new federal act.

It was heard by the Committee on Public Health on April 13.

H. 287 (revised). Bill providing for a marriage protection law by requiring a physician's examination and certificate before issuance of marriage licenses. This bill was proposed by Rep. Cutler and in its revised form is now favored by your committee.

It was heard before the Committee on Public Health on March 28.

H. 670. Bill providing for the issuance of certificates of approval of bacteriological laboratories by the Department of Public Health. The bill was proposed by the Massachusetts Public Health Association and is similar to the one favored by the Massachusetts Medical Society last year.

This bill was reported favorably by the Committee on Public Health and sent to the Committee on Ways and Means.

H. 852. Bill requiring licensing of hospitals, convalescent homes and nursing homes. This bill was proposed by the Massachusetts Central Health Council and provides for the Department of Public Health to set up certain standards of health and enforce them.

This bill has been favorably reported by the Committee on Public Health and referred to the Committee on Ways and Means.

H. 1407. Bill prohibiting aliens from practicing medicine. This bill was proposed by Rep. Vaughan and is poorly written. It provides that no license be granted to an alien until his first papers have been filed but allows certain very broad exceptions.

This bill was heard by the Committee on Public Health on March 14. An amended bill has been presented.

OPPOSE

H. 551. Bill requiring that notices of intention of marriage shall be accompanied by a physician's certificate that neither party is infected with syphilis. This bill was proposed by Dr. William Frankman and also needs major revision before being satisfactory.

A report of leave to withdraw has been filed in the House.

H. 758. Bill providing authority to the Board of Registration of Nurses to limit further training of nurses of all classes and attendants under certain conditions. The bill was proposed by Miss Josephine E. Thurlow but is against public policy.

It was heard by the Committee on Public Health on February 2 and again on March 7.

H. 759. Bill providing for training and licensing of first-class bedside nurses. This bill was proposed by Miss Josephine E. Thurlow, but is against public policy.

It was heard by the Committee on Public Health on February 2 and again on March 7.

H. 858. Bill regulating the practice of nursing. This bill was proposed by the Massachusetts State Nurses Association, and while it is better than last year's bill, some of last year's defects are still present.

It was heard by the Committee on Public Health on February 2 and again on March 7.

H. 985. Bill requiring doctors of medicine and doctors of osteopathy on the Board of Registration in Medicine. This bill was proposed by the Massachusetts Osteopathic Association and would put two osteopathic physicians on the Board.

This bill has been given leave to withdraw.

H. 986. Bill providing for a doctor of medicine and a doctor of osteopathy on the Approving Authority and the status of approvals by the American Medical Association and the American Osteopathic Association. This bill was proposed by the Massachusetts Osteopathic Association; it weakens the Approving Authority.

This bill has been given leave to withdraw.

H. 1401. Bill providing that certificates of vaccination or non-vaccination shall no longer be required as a prerequisite to the attendance of any child in public schools. This is a typical anti-vaccination bill.

This bill has been given leave to withdraw.

H. 1898. Bill providing for the establishment and administration of a system of health insurance. This bill was proposed by the State Industrial Council of the Congress of Industrial Organization (C.I.O.) and means complete state insurance medicine with a 4½ per cent pay-roll tax. It represents real regimentation of physicians.

This bill has been given leave to withdraw.

CHARLES C. LUND, *Chairman,*
Committee on State and
National Legislation.

DEATHS

McCREA — ALBERT J. McCREA, M.D., of 284 Main Street, Southbridge, died April 28. He was in his sixty-ninth year.

Born in Winchendon, he received his degree from the Eclectic Medical College, Cincinnati, Ohio, in 1894. Dr. McCrea was a director of the Masonic Hospital in Shrewsbury.

He was a member of the Massachusetts Medical Society, the American Medical Association and the Medical Examiners' Association.

His widow, a son and a sister survive him.

SCHORER — CORNELIA B. J. SCHORER, M.D., of Foxboro, died in Berlin, Germany, January 9.

Dr. Schorer received her degree from the Universität Zurich Medizinische Fakultät, Switzerland, in 1897. Before her retirement in 1933 she was a member of the resident medical staff of the Foxborough State Hospital.

She was a fellow of the Massachusetts Medical Society and the American Medical Association and was a member of the American Psychiatric Association and the New England Society of Psychiatry.

WILLIS — JOHN E. WILLIS, M.D., of Worcester, died April 21. He was in his sixty-fifth year.

Born in East Bridgewater, he received his degree from Boston University School of Medicine in 1898. After practicing in Somersworth, New Hampshire, for one year he attended the New York University College of Medicine, studying electrotherapy. In recent years he had continued studies in this specialty at Boston University. In 1903 he went to Worcester and shortly afterward became associated with the Hahnemann Hospital, where he was a staff physician at the time of his death.

Dr. Willis was a fellow of the Massachusetts Medical Society and the American Medical Association and was a member of the American Institute of Homeopathy and the Massachusetts Homeopathic Society.

His widow, a sister and two brothers survive him.

MISCELLANY

THE CYTOLOGY OF SPUTUM

When the practitioner sends a sputum specimen to the laboratory he expects usually to learn only whether or not tubercle bacilli are present. Much more can be learned by a careful study of the sputum, as Dr. S. Roodhouse Gloyne, pathologist at the London Chest Hospital, whose work has attracted widespread attention, has shown in the following article, which was prepared especially for *Tuberculosis Abstracts* and appeared in the May issue.

* * *

We are all apt to assume that everything that goes into a sputum cup is sputum. Saliva, postnasal and pharyngeal secretions which have trickled down the throat, even gastric contents resulting from retching may be confused with true sputum. The word will be taken here to mean the material which coughing ejects from the respiratory passages. Cytological examination often enables us to determine from what part of the respiratory tract the secretion comes and what its nature is.

Specimens should be as fresh as possible, because cells degenerate more quickly than do bacteria and a stale specimen is valueless for cytological purposes. The next thing is to select suitable portions for examination. There is only one safe rule, namely to select every portion which looks different in appearance from any other portion — mucoid, purulent, pigmented, blood-stained, gelatinous, and so forth. The purulent portion is the least useful. The specimen may be poured into a wide dish (an ordinary bacteriological Petri dish) and placed on a light or dark background as required. It is not enough to take a

wild plunge at an evil-smelling specimen with a platinum loop and to trust to luck. Each portion should be picked out with sterile forceps, and placed upon one end of a slide. A thin film is then made with the edge of another slide in the same way that one spreads a blood film for malaria parasites. In selecting the portions it is a good plan to go over the specimen carefully first with a hand lens. The technic used by the writer for staining films is a modification of that of Dudgeon and Wrigley: (1) fix wet films in Schaudinn's solution (absolute alcohol, 1 part, saturated aqueous solution of mercury bichloride, 2 parts, with 3 per cent acetic acid added immediately before use) for five minutes; (2) pour off fixative and cover with 0.5 per cent iodine in 70 per cent alcohol for two or three minutes; (3) drain off this solution and cover with the following solution for two or three minutes: sodium thiosulfate, 7.5 gm.; 96 per cent alcohol, 100 cc.; distilled water, 450 cc.; (4) wash and stain with undiluted Delafield's hematoxylin for two or three minutes; (5) pour off stain and differentiate with 1.0 per cent hydrochloric acid; (6) counterstain with Biebrich's scarlet or orange G; (7) dehydrate with absolute alcohol, clear with xylol and mount in neutral balsam.

The cells encountered may be classified into three groups: cells which have migrated from the blood stream; tissue cells from various portions of the respiratory tract; abnormal cells resulting from various types of growth.

The cells of the first group are leukocytes and erythrocytes, and they are found in practically all sputums. The neutrophil polymorphonuclear cell is an essential part of the tissue response in all suppurative diseases of the lung. It is fundamentally a phagocyte and frequently contains organisms. After Lipiodol administration it will show engulfed oil droplets also. The predominance of the lymphocyte, which is such a useful diagnostic sign of tuberculosis in other exudates, is in the writer's view quite valueless in sputum. Lastly there is the eosinophil cell, commonly found in asthma.

Of the tissue cells, the commonest is the transitional squamous cell which covers the anterior surface of the epiglottis, the upper half of the posterior surface, the aryo-epiglottic folds and vocal cords and the pharynx. This cell is generally found in association with large numbers of the organisms of the catarrhal infections. A cytologic picture of this kind is common in the chronic catarrhs of the winter months. The ciliated columnar cell of the epithelium of the respiratory tract extends from the trachea down to the small bronchi and may desquamate and appear in the sputum when the mucosa is ulcerated. It is often seen after the passage of a bronchoscope. The lining cells of the respiratory bronchioles and alveolar ducts are of a low cuboidal non-ciliated type, and they are not easy to distinguish from other mononuclear cells in sputum unless they are adhering together in plaques. *None of the cells in this group are phagocytes.* There is, however, a cell, conveniently considered here, which does phagocyte, namely the macrophage. It masquerades under many names, the heart-failure cell, the dust cell, and so forth, but is really part of the reticuloendothelial system and is an expert phagocyte. It is found in pulmonary tuberculosis, the pneumoconioses, chronic congestive failure and pulmonary edema, and may contain tubercle bacilli, carbon pigment, red-blood cells or hemoglobin pigment, as the case may be. The refractile particles of quartz or asbestos found in the pneumoconioses cannot be seen in the ordinary stained specimen.

With regard to the third group, excluding the hepatic cells of ruptured liver abscess and the lymphadenoma cell of Hodgkin's disease, which the writer has seen in sputum on only one or two occasions, the cells of this group are neoplastic. In the case of secondary growths of the lung, any form of cell which is found in the primary growth may, of course, appear in the sputum, but in the primary malignant growths of the lung the cells for practical purposes arise from only two kinds of tumor, the oat-cell carcinoma and the squamous carcinoma. The oat-cell carcinoma is generally associated with a primary massive growth of the mediastinal nodes, and although this growth exerts great pressure on the main bronchi, it does not as a rule ulcerate and break down. The oat-cell, therefore, is not commonly found in sputum. Moreover, it is difficult to differentiate from granulation-tissue cells and fibroblasts from the bronchial wall. This cell, therefore, should be diagnosed with the very greatest circumspection.

The squamous carcinoma cell is derived from bronchial growths. It is not sufficiently realized that bronchial carcinoma breaks down into cavity with even greater regularity than a tuberculous lesion. A single pulmonary abscess developing insidiously in a person of middle age without obvious cause is more likely than not to be due to a breaking down of a bronchial carcinoma. This cell can be found readily in the sputum but must be carefully distinguished from the normal transitional squamous cell of the upper respiratory tract. It is usually found adhering to its neighbors in small plaques, the individual cells of which exhibit marked diversity of form and size. In the early stage of its growth the cell shows a rounded nucleus with an open chromatin network, a large nucleolus, and a more or less clear cytoplasm with a cell envelope attached to its neighboring cell along the contiguous border, and prickle-cell arrangement. As the cell develops, vacuolation takes place and the nucleus is pushed to one side until it eventually comes to occupy a position near the cell envelope and is squeezed into a horseshoe shape. Keratinization of the cell follows, and the cytoplasm stains darker in consequence. All these stages may be found in the different cells of one plaque, and when keratinization occurs, it is possible to identify individual squamous carcinoma cells irrespective of plaque formation. Cell nests are rarely found in sputum films. The carcinoma cell does not phagocyte — a cardinal point in distinguishing it from the macrophage with which it is very easily confused in the early stage of neoplastic growth.

Space does not permit of a description of wet films and of frozen and paraffin sections, but the stained-film method outlined above will amply repay careful study. It is possible thus to make a diagnosis of asthma, bronchial ulceration and chronic pulmonary edema, while it is of the greatest value in detecting bronchial carcinoma and will even enable one sometimes to gain corroborative evidence of pulmonary tuberculosis. The broad way to failure is to take the first portion of sputum which presents itself; the straight and narrow way to success is to go over the specimen with a hand lens and select the particles for examination with discrimination. *Experientia docet.*

MAINE NEWS

Annual Meeting

The eighty-seventh annual meeting of the Maine Medical Association will be held at Poland Springs, Sunday, Monday and Tuesday, June 25, 26 and 27.

The central location of Poland Springs makes it the ideal situation for this meeting. The new management has granted reduced hotel rates, with free parking of automobiles. Golf fees will be only one dollar for all-day playing. An orchestra will be available at dinner for entertainment and dancing. There will be an entertainment on Sunday evening.

The usual conferences will be held Monday and Tuesday mornings, but they will differ from those in the past in that several physicians will participate as leaders; each conference will run from 9:30 to 12 noon. There will be a clinicopathological session Monday afternoon. Monday evening a speaker from New York — name to be announced — will address the meeting. Three nationally known physicians will speak on Tuesday afternoon. Dr. Morris Fishbein, editor of the *Journal of the American Medical Association,* will be the speaker on Tuesday evening. Medical moving pictures will be provided, and special entertainment for the ladies.

Women's Field Army

The Women's Field Army reports that from January 23 to March 21 seventy-three districts were organized for complete participation in the 1939 educational campaign. This is most encouraging in view of the fact that almost all of this was done by mail. Every county is represented in the units organized.

In addition to the districts organized for active participation thirty will be covered by direct mail appeals and personal solicitations. Of this total, twelve districts have never participated in previous campaigns. With the permission of the Maine Medical Association and of Dr. Edward H. Risley, chairman of the State Advisory Board, copies of the very fine editorial on the Women's Field Army, which appeared in the February issue of the *Journal of the Maine Medical Association,* were sent to all the daily newspapers and several of the weeklies, with the request that it be reprinted or that an article based upon it be given. This is bringing a most gratifying result and should answer conclusively the questions sometimes asked about the attitude of the physician and the Association toward the work of the Women's Field Army.

County Meetings

On April 11, Dr. S. J. Thannhauser, of Boston, talked before the Knox County Medical Society; the title was "Vitamin Deficiencies."

The Kennebec County Medical Society was addressed by Dr. Samuel Levine, of Boston, on April 20, the title of his talk being "Auscultation of the Heart."

On April 21, Dr. Richard H. Overholt, of Boston, talked before the Cumberland County Medical Society; his topic was "Some New Developments in the Management of Chest Lesions."

Notes

The following physicians have recently become members of the Maine Medical Association: D. Foster, of Portland; Albert S. Owen and E. M. Fuller, of Bath; H. Grubin, of Lubec.

The following new panel discussions have been added to the list available for the county medical societies:

Cancer: Dr. Edward H. Risley, chairman, Waterville.
Thoracic Surgery: Dr. George E. Young, chairman, Skowhegan.

The Maine Public Health Association is conducting a "Help Find Early Tuberculosis" campaign, urging people to become "tuberculosis-conscious and tuberculosis-suspicious" in order to cut down the large number of cases of advanced tuberculosis now being admitted to our sanatoriums.

A course in allergy is open, on application, to physicians of Maine under the auspices of the Bingham Associates. A fee of $25 is charged for the course, which is of one week's duration, but a fellowship fee of $50 is allowed and a physician taking the course may obtain room and board at the hospital for $10. Full information is available from Dr. F. T. Hill, Waterville, or Dr. Fred R. Carter, 22 Arsenal Street, Portland.

A teaching clinic was held at the Central Maine General Hospital on April 28, under the direction of Dr. John Fraser, professor of obstetrics and gynecology, McGill University Faculty of Medicine, Montreal. A clinic was held in the morning, and ward rounds in the afternoon. In the evening Dr. Fraser discussed "The Treatment of Hemorrhage in Late Pregnancy."

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1939

DISEASES	MARCH 1939	MARCH 1938	FIVE-YEAR AVERAGE*
Anterior poliomyelitis	0	0	0
Chickenpox	1181	1944	1341
Diphtheria	14	17	28
Dog bite	765	781	686
Dysentery, bacillary	24	0	2
German measles	105	92	1238
Gonorrhea	384	463	482
Lobar pneumonia	900	654	652
Measles	4290	1259	4154
Meningococcus meningitis	5	9	19
Mumps	1015	1303	1185
Paratyphoid B fever	1	8	2
Scarlet fever	901	1712	1295
Syphilis	416	635	543
Tuberculosis, pulmonary	345	291	315
Tuberculosis, other forms	30	39	41
Typhoid fever	4	3	5
Undulant fever	3	4	2
Whooping cough	971	573	1146

*Based on figures for preceding five years.

RARE DISEASES

Diphtheria was reported from: Boston, 3; Cambridge, 1; Lawrence, 2; Medford, 1; Methuen, 2; Shrewsbury, 1; Taunton, 1; Woburn, 1; Worcester, 2; total, 14.

Dysentery, bacillary, was reported from: Boston, 1; Lowell, 1; Wrentham, 22; total, 24.

Infectious encephalitis was reported from: Arlington, 1; Chicopee, 1; Norfolk, 2; total, 4.

Meningococcus meningitis was reported from: Boston, 1; Gardner, 1; Southbridge, 1; Springfield, 2; total, 5.

Paratyphoid B fever was reported from: Malden, 1; total, 1.

Pfeiffer bacillus meningitis was reported from: Everett, 1; Lowell, 1; total, 2.

Septic sore throat was reported from: Belmont, 2; Boston, 11; Fall River, 1; Lawrence, 1; Malden, 3; Taunton, 1; Wenham, 4; Westwood, 1; total, 24.

Trachoma was reported from: Boston, 1; Milford, 1; Watertown, 1; Webster, 1; total, 4.

Typhoid fever was reported from: Boston, 2; Framingham, 1; Saugus, 1; total, 4.

Undulant fever was reported from: Gardner, 1; Kingston, 1; Lowell, 1; total, 3.

Lobar pneumonia, pulmonary tuberculosis, measles and undulant fever were reported above the five-year average.

Scarlet fever, diphtheria, German measles, chickenpox and mumps were reported below the five-year average.

Tuberculosis (other forms) showed record low figures for the third consecutive month.

Whooping cough, meningococcus meningitis and typhoid fever were reported below the five-year average.

Animal rabies showed record low incidence for the fourth consecutive month. Foci in Canton and Haverhill were active.

CORRESPONDENCE

LICENSE SUSPENDED

To the Editor: The license of Dr. Roland O. Parris, of Falmouth, was suspended for one month from April 20, 1939, because of negligence in the postoperative care of a patient.

STEPHEN RUSHMORE, M.D., *Secretary,*
Board of Registration in Medicine.

State House,
Boston.

REFERENCE STANDARD FOR THIAMIN CHLORIDE (VITAMIN B_1)

To the Editor: Synthetic Crystalline Vitamin B_1 has now been made the U.S.P. reference standard for what has long been known as Vitamin B_1 but is now called Thiamin Chloride, and this reference standard is now available, having been supplied by the U.S.P. Board of Trustees, with the co-operation of the U.S.P. Vitamin Advisory Board. Orders for this new reference standard should be sent to the chairman of the Committee of Revision, 43rd Street and Woodland Avenue, Philadelphia.

Thiamin Chloride, as a crystalline substance, has been proposed for inclusion in the Second U.S.P. XI Supplement. If it is admitted, the physical and chemical tests will be sufficient to determine its quality and therapeutic activity but when present in preparations or in solution, or when a part of the "vitamin B complex," its activity will have to be determined by the biological assay procedure recommended for official adoption.

E. FULLERTON COOK, *Chairman,*
U.S.P. Committee of Revision.

43rd Street and Woodland Avenue,
Philadelphia.

SULFANILAMIDE AND DESQUAMATION OF THE SKIN

To the Editor: For the past few months there has been considerable controversy between attending physicians and health authorities regarding children who have suffered from slight pharyngeal disturbances and who have later shown desquamation of the skin. Because of the possibility of their having had scarlet fever, these children have been sent home by school physicians, with loss of time from school and mental annoyance to the parents and attending physicians.

Recently I saw two cases of desquamation of the skin following the use of sulfanilamide. I think it would be well for medical inspectors of the health department to inquire whether or not such children had received sulfanilamide at the time of their illness, for the use of this drug might solve the mysterious desquamation of the skin, provided the attending physician were certain that there was no possibility of the disease's having been scarlet fever. At the present time, sulfanilamide is being given for almost every acute infection.

JOHN G. DOWNING, M.D.

520 Commonwealth Avenue,
Boston.

REPORTS OF MEETINGS

ALPHA OMEGA ALPHA LECTURE

At a regular lecture sponsored by the Harvard chapter of Alpha Omega Alpha, on Monday, January 16, at the Harvard Medical School, President Donald Matson introduced the guest speaker, Dr. Eugene F. DuBois of the Russell Sage Institute of Pathology, Cornell Medical College, and the New York Hospital. Dr. DuBois spoke on "Heat Loss from the Human Body."

Dr. DuBois described how he came to be interested in this study. His work in this field began twenty-three years ago with Dr. Joseph C. Aub, and they established some standards of basal metabolism based on body surface area. Receiving further stimuli from problems in air-conditioning and malaria therapy, the Russell Sage investigators six years ago decided to limit their field to the study of heat loss.

Dr. DuBois presented lantern-slide charts to show a normal twenty-four hour curve of heat production and loss. On waking in the morning, one's heat loss is almost equal to one's heat production, both being at a low level. The subject of the experiment took a short run; the heat production curve went up steeply but the heat loss curve lagged far behind, which meant that heat was being stored. The subject returned to rest and to take a cold shower, whereupon the loss of body heat became much greater than its production. When the subject went to bed at night, the curves gradually dropped to the equal low level at the start of the experiment.

The process was described as a balanced scale, with the pointer representing body temperature at 37°C. Heat loss, on a foundation of radiation, convection and vaporization, is favored by such factors as a cooler environment, increased skin circulation and an increase in sweating and panting, which will swing the balance toward lower temperatures. On the other side of the scale is heat production, based on fundamental oxidation of carbohydrate, fat and protein, and made variable by excitement, exercise, increased basal metabolic rate, and so on, and tending to move the pointer toward higher temperatures.

The factors involved in loss of body heat can be divided into physical and physiological ones. In considering the physical factors, it should be appreciated that man's specific heat being 0.82, which is lower than that of water, a temperature rise of 1°C. in a 70-kg. man requires the addition to the body of 57 calories. The skin has extraordinary heat-insulating properties; compared with the conduction value of cork, which is 0.0007, epidermis, muscle and fat have values from 0.00047 to 0.00050. Man, in addition, has the power of changing the properties of his skin. A 70-kg. man has 1.8 square meters of surface area and a temperature gradient from within outward of 1.8°C. to 10 cm. in depth. The skin is a 99-per-cent-perfect black-body radiator, there being not much difference between the skins of Negroes and Whites. The amount of moisture exuded is also a factor.

The physiological factors deal with the vascular, nervous and endocrine systems. Blood flow from within outward transports heat to the surface. Over the veins one can detect colder streaks moving inward. The body is particularly able to control heat production and dissipation, and the amount of moisture in the skin. The skin is extremely sensitive to temperature changes; for example, the skin of the forehead has been found able to detect within two or three seconds a temperature change of 0.003°C.

Dr. DuBois then took time to review briefly the literature on the subject to show how the study depended on the development of measuring instruments for determining values of heat loss by radiation, convection and vaporization. These are governed by physical laws. At the start of the work, he had difficulty in measuring convection, and Dr. James G. Hardy, a physicist, was asked to

contribute his efforts. Dr. Hardy invented the radiometer, which Dr. DuBois proceeded to describe. It measures radiation heat, which comes in the 5 to 20 μ wavelength zone, and also skin temperatures, since the skin is almost a perfect black-body radiator.

In 1934 Dr. DuBois began experiments with the purpose of reducing variables to a minimum value. This required the accumulation of data on many people as subjects. He described the procedure in obtaining these readings before giving the results obtained. The remainder of his presentation consisted of the results of such experiments.

It was found that at an environmental temperature of 22°C. the feet were much colder than the head and the toes even colder than the air. The toes are good heat dissipators by their surface area and sweating, and they are a long distance from the central heating. However, as the room temperature warmed toward 35°C., these areas more nearly approached each other in warmth, the greatest rise in temperature being in the feet and toes.

The breaking down of data obtained in a series of such experiments into components of radiation, convection and vaporization, revealed that with a change in temperature from 20 to 35°C. the amount of heat loss by radiation declined to zero, as did the amount by convection, but not so regularly, and that heat loss by vaporization increased. The region of balance was at 28 to 30°C.; this can be called the "comfort zone," in which heat loss equals heat production and the body is easily able to control loss by means of its vasomotor apparatus. At the 22°C. end of the scale, heat loss is much greater than heat production, and what the body can do in the way of reducing vaporization to a minimum still is not enough, since radiation and convection are beyond control at this point. At the warmer end of the scale, heat loss is a little greater than heat production, on account of a temporary overcompensation by vaporization.

A comparison of men and women reveals the interesting fact that in men heat production is relatively constant, though heat loss may change, whereas in women at air temperatures of 28 to 36°C. the rate of heat production seems to parallel closely the rate of heat loss.

Further experiments studied work, malarial chills and the use of a fan. During a chill, the rate of heat production goes up. A fan turned on the subject in a room as warm as himself will make him feel more comfortable, although actually the components of heat loss do not change their values at all!

Dr. DuBois concluded by describing what goes on in a game of squash racquets. During the game, heat production rises tremendously and the rectal temperature of the contestant goes from 37 to 39°C.; however, the temperature of the skin falls. The value for radiation goes down; that for convection rises moderately; heat loss by vaporization is tremendously increased and remains high during the after-game rest period. Thirty-six minutes after the game ends, the rectal temperature is back to normal and the skin temperature rises from its low level. This proves that excess heat is lost from a cool skin rather than from a warm one.

Dr. DuBois illustrated dramatically the curves made by heat production and heat dissipation during and after this game of squash. Heat production during violent exercise rises in the direction of carbohydrate metabolism faster than heat loss rises in the direction of vaporization, and during the rest period following falls back to normal faster than does heat loss.

NOTICES

TUMOR CLINIC, BOSTON DISPENSARY

Each Tuesday and Friday morning, 10:00 to 12:30, there is a meeting of the Tumor Clinic of the Boston Dispensary, a unit of the New England Medical Center. Neoplasms of various sorts are seen and discussed, and when there is an indication, are treated with radium of high-voltage x-ray. Physicians are invited to visit this clinic. They may bring patients for aid in diagnosis or may refer patients to the clinic following which a report will be returned to the referring physician. A limited number of beds are available for diagnostic study and for treatment.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Dr. A. A. Berg, of the Mount Sinai Hospital, New York City, will discuss "The Surgical Aspects in the Management of Ulcerative Colitis" on Tuesday morning, May 9, from 9:00 to 10:00. Dr. K. S. Andrews and Dr. Henry Lerner will discuss the secondary manifestations.

BOSTON CITY HOSPITAL

The monthly clinicopathological conference will be held at the Boston City Hospital on Wednesday, May 10, at 12 o'clock noon, in the Pathological Amphitheater.

JOSEPH E. HALLISEY, M.D., *Secretary,*
Medical Staff.

NORFOLK DISTRICT MEDICAL SOCIETY

The eighty-ninth annual meeting of the Norfolk District Medical Society will be held at the Hotel Somerset, Boston, on Wednesday, May 10.

The business meeting will begin at 6:00 p. m.; dinner will be served at 6:45. Following the dinner, there will be a talk by Mr. James H. Powers, editor of foreign affairs for the *Boston Globe,* whose subject will be: "American Foreign Policy Comes of Age."

DAVID D. SCANNELL, M.D., *President,*
FRANK S. CRUICKSHANK, M.D., *Secretary.*

MASSACHUSETTS ITALIAN MEDICAL SOCIETY

The regular meeting of the Massachusetts Italian Medical Society will be held at the Hotel Kenmore, Boston, on Friday evening, May 26, at 9:00. Dr. Elliott C. Cutler will speak on "Biliary Surgery: Including diagnosis and treatment."

A general discussion will follow. The medical profession is cordially invited to attend.

CARL F. MARALDI, M.D., *Secretary.*

NEW ENGLAND OBSTETRICAL AND GYNECOLOGICAL SOCIETY

The eleventh annual spring meeting of the New England Obstetrical and Gynecological Society will be held in Portland, Maine, on Wednesday, May 24.

NATIONAL HOSPITAL DAY

National Hospital Day will again be observed in all the New England hospitals on Friday, May 12. Open house will be observed in some hospitals, while special programs

and exhibits will be put on by others. The committee for New England consists of the National Hospital Day chairmen from each of the New England states.

Radio programs have been arranged through Stations WEEI, WAAB, and WCOP, as follows:

May 10. 9:30 a. m. Station WAAB. A round table discussion by Dr. Warren Cook, superintendent of the New England Deaconess Hospital, and Dr. Joseph P. Leone, superintendent of the Quincy City Hospital and chairman of National Hospital Day for Massachusetts and New England, under the auspices of the Massachusetts Department of Public Health.

Topic: "The Community Hospital and National Hospital Day."

May 11. 7:00–7:30 p. m. Station WCOP. A round table discussion by the state chairmen from all the New England states.

Topic: "The Modern Hospital."

May 12. 4:00 p. m. Station WEEI. National Hospital Day.

Speakers: Mr. Edward Dana, director of Associated Hospital Service Corporation of Massachusetts, and Dr. Charles Wilinsky, director of the Beth Israel Hospital.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Monday, May 8

Tuesday, May 9

*9-10 a. m. Ulcerative Colitis. Dr. A. A. Berg, Dr. K. S. Andrews and Dr. Henry Lerner. Joseph H. Pratt Diagnostic Hospital.

*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

Wednesday, May 10

*9-10 a. m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital amphitheater.

12 m. Monthly clinicopathological conference. Boston City Hospital. Pathological amphitheater.

6 p. m. Norfolk District Medical Society. Hotel Somerset, Boston.

Thursday, May 11

*9-10 a. m. Macrocytic Anemia and Liver Therapy. Dr. W. P. Murphy. Joseph H. Pratt Diagnostic Hospital.

Friday, May 12

National Hospital Day.

*9-10 a. m. Medical Aids to Crime Detection. Dr. E. V. Hill. Joseph H. Pratt Diagnostic Hospital.

*10 a. m. - 12:30 p. m. Tumor clinic. Boston Dispensary.

12 m. Clinical meeting of the Children's Medical Service. Massachusetts General Hospital. Ether Dome.

Saturday, May 13

*9-10 a. m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*10 a. m. - 12 m. Staff rounds of the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.

May 7 — Health Lecture, Quincy City Hospital. Page 636, issue of February 23.

May 7-15 — International Congress of Military Medicine and Pharmacy. Page 501, issue of September 29.

May 9 — Joseph H. Pratt Diagnostic Hospital. Page 768.

May 10 — Monthly clinicopathological conference, Boston City Hospital. Page 768.

May 11 — Pentucket Association of Physicians, 8:30 p. m., Hotel Bartlett, 95 Main Street, Haverhill.

May 12 — National Hospital Day. Page 768.

May 12 and 13 — American Heart Association. Page 542, issue of March 23.

May 13-16 — American Board of Obstetrics and Gynecology. Page 457, issue of March 9.

May 14-20 — American Physicians' Art Association. Page 404, issue of March 2.

May 15-19 — American Medical Association. St. Louis, Missouri.

May 22, 23, and 24 — American Association for the Study of Goiter. Page 405, issue of March 2.

May 24 — New England Obstetrical and Gynecological Society. Page 768.

May 26 — Massachusetts Italian Medical Society. Page 768.

June 5, 6, 7, and 8 — American Association of Industrial Physicians and Surgeons. Page 581, issue of March 30.

June 6, 7, and 8 — Massachusetts Medical Society. Worcester.

June 12-17 — Symposium on the Public-Health Significance of the Virus and Rickettsial Diseases. Page 125, issue of January 19.

June 26-29 — National Tuberculosis Association. Page 936, issue of December 8.

September — Boston Psychoanalytic Institute. Page 450, issue of September 22.

September 11-15 — American Congress on Obstetrics and Gynecology. Page 938, issue of December 8.

September 15-28 — Pan-Pacific Surgical Association. Page 863, issue of November 24.

October 23 - November 3 — New York Academy of Medicine. Page 581, issue of March 30.

Fall, 1939 — Temperature Symposium. Page 218, issue of February 2.

District Medical Societies

ESSEX SOUTH

May 10 — Page 649, issue of April 13.

NORFOLK

May 10 — Page 768.

WORCESTER

May 10 — Worcester Country Club — annual meeting.

BOOKS RECEIVED FOR REVIEW

You Can't Eat That! A manual and recipe book for those who suffer either acutely or mildly (and perhaps unconsciously) from food allergy. Helen Morgan. 330 pp. New York: Harcourt, Brace & Co., 1939. $2.50.

The Principles and Practice of Ophthalmic Surgery. Edmund B. Spaeth. 835 pp. Philadelphia: Lea & Febiger, 1939. $10.00.

The Circulation of the Brain and Spinal Cord: A symposium on blood supply. The proceedings of the Association for Research in Nervous and Mental Disease, New York, December 27 and 28, 1937. 790 pp. Baltimore: Williams & Wilkins Co., 1938. $10.00.

Failure of the Circulation. Tinsley R. Harrison. 502 pp. Baltimore: The Williams & Wilkins Co., 1939. $4.50.

The Clinical Diagnosis of Swellings. C. E. Corrigan. 313 pp. Baltimore: The Williams & Wilkins Co., 1939. $4.00.

Thus We Are Men. Walter Langdon-Brown. 344 pp. New York: Longmans, Green & Co., 1939. $3.50.

Holmes of the Breakfast-Table. M. A. D. Howe. 171 pp. London and New York: Oxford University Press, 1939. $2.50.

Traité de Biocolloïdologie. Tome V. *État Colloïdal et Médecine.* Fascicule 1. *Le Sang.* W. Kopaczewski. 151 pp. Paris: Gauthier-Villars, 1937. 60 Fr. fr.

Traité de Biocolloïdologie. Tome V. *État Colloïdal et Médecine.* Fascicule 2. *Liquides et Tissus Organiques.* W. Kopaczewski. 299 pp. Paris: Gauthier-Villars, 1938. 100 Fr. fr.

Sleep, Your Life's One Third. Maurice Chideckel. 183 pp. New York: The Saravan House, 1939. $2.00.

Preclinical Medicine: Preclinical states and prevention of disease. Malford W. Thewlis. 223 pp. Baltimore: The William & Wilkins Co., 1939. $3.00.

Hypertension and Nephritis. Arthur M. Fishberg. Fourth edition, thoroughly revised. 779 pp. Philadelphia: Lea & Febiger, 1939. $7.50.

Manual of Toxicology. Forrest R. Davison. 241 pp. New York: Paul B. Hoeber, Inc., 1939. $2.50.

Community Health Organization: A manual of administration and procedure primarily for urban cases. Edited by Ira V. Hiscock. Third edition. 318 pp. New York: The Commonwealth Fund, 1939. $2.50.

Les Calculs de l'Uretère. Pierre Macquet. 186 pp. Paris: Masson et Cie, 1939. 45 Fr. fr.

Les Erreurs et les Fautes en Urologie. L. Strominger. 176 pp. Paris: Masson et Cie, 1939. 45 Fr. fr.

Actualités Médico-Chirurgicales. Par les chefs de clinique de la Faculté de Médecine de Marseille. Quatrième série. 192 pp. Paris: Masson et Cie, 1939. 30 Fr. fr.

Studies on Pain Conduction in the Trigeminal Nerve: A contribution to the surgical treatment of facial pain. Olof Sjöqvist. 139 pp. New York: G. E. Stechert & Co., 1938. $3.00.

Angina Pectoris: Nerve pathways, physiology, symptomatology, and treatment. Heyman R. Miller. 275 pp. Baltimore: The Williams & Wilkins Co., 1939. $3.25.

BOOK REVIEWS

Drug Addicts Are Human Beings: The story of our billion-dollar drug racket — how we created it and how we can wipe it out. Henry S. Williams. 273 pp. Washington: Shaw Publishing Co., 1938. $2.50.

Probably most people who read this book will be surprised to learn the estimated number of morphine addicts in the United States and the number of reputable physicians who have been imprisoned or have paid fines because of convictions in courts for the alleged illegal treatment of these addicts.

One rarely finds a more zealous enterprise to bring about a reform than that shown in this volume where the author tries to convince doctors that the victims of the morphine habit are sick persons worthy of medical treatment. He also tries to teach lawyers and judges that the Harrison Narcotic Act has been misunderstood and misapplied by agents of the Narcotic Bureau in dealing with the problems involved in the medical care of addicts.

Quotations of decisions of the Supreme Court of the United States are presented and show that the Harrison Narcotic Act as drawn and amended is a revenue measure only, and that nothing in the law justifies the prosecution of reputable physicians who have treated morphine addicts. The assumption of certain judges and lawyers that the regulations of the Narcotic Bureau with respect to prescribing appropriate doses of morphine to addicts outside of jails and government hospitals has the force of law is also found to be unsound. This interpretation of the regulations has led to the closing of well-organized clinics served by well-qualified doctors, and the imposition of fines and jail sentences on many reputable physicians. Because of these court actions, doctors have declined to treat these addicts, with the result that these unfortunate people have been led to deal with the dope peddlers and thus there has been established the so-called "billion-dollar racket."

The purveyors of the drug charge a dollar or more for a grain of morphine, whereas when the drug is dispensed under medical care the price is only a few cents. This deplorable situation prevents the effective treatment of ambulatory addicts and perpetuates the racket; under properly regulated medical treatment the peddler would go out of business.

The Narcotic Bureau seems to have found it easier to convict a doctor even if he prescribed properly regulated doses for an addict than to eliminate the peddler. According to Dr. Williams it seems to be more gratifying for the bureau to prosecute a doctor than to deal with the real criminal. The situation seems to have changed for the better since the action of two federal judges as detailed in this book, who, after careful study of the situation, have rendered decisions to the effect that there is no legal justification for the prosecution of doctors who have treated morphine addicts with the purpose of meeting the medical problems involved. With these two decisions the author contends that a logical method of dealing with the situation will be brought about which will return the addict to medical care and the peddler will be deprived of his income and retire from the field. This may be utopian, but the arguments advanced are interesting.

The author does not hesitate to use sarcasm of a high order in his vigorous denunciation of mistaken policies of the Narcotic Bureau and the methods employed by its officials. The book is well written, contains much information and the arguments seem to be sound.

With the facts before the public the question arises as to the position of organized medicine in efforts to have abuses eliminated and logical procedures adopted.

Classic Descriptions of Disease: With biographical sketches of the authors. Ralph H. Major. Second edition. 727 pp. Springfield, Illinois, and Baltimore: Charles C Thomas, 1939. $5.50.

This well-known book was first issued in 1932 and had a wide circulation. It was deservedly popular for nothing of its type was available in English. At the time it was issued, the book was criticized on the basis of its incompleteness and the numerous mistakes in dates and sometimes actually in text. With the new edition, the author has not only revised his texts but he has carefully checked dates and references. In many places, moreover, the translations have been improved, although occasionally they leave something to be desired. The principal change in the second edition, however, is the added material. For this, every student of the history of medicine will be grateful. There are new sections on malaria and yellow fever. The biographical sketches have, in part, been re-written and the index completely revised. This edition can be more highly recommended than the first.

Hygiene: Manual of public health. J. R. Currie. 324 pp. Baltimore: William Wood & Co., 1938. $5.00.

Although this book is designed for the instruction of medical students, practitioners interested in personal and public hygiene will find useful information in every chapter.

Beginning with a brief account of the early efforts to interest people in the underlying principles relating to personal and community health, the subsequent chapters explain hereditary and environmental factors which affect the well-being of the human race. The details of the public-health administration of Great Britain are set forth. Chapters devoted to the etiology and treatment of infections and communicable diseases are well written and will be useful for reference. That part devoted to the poison gases used in warfare, with precautions to be observed, are timely under existing conditions on the other side of the ocean.

The author is an authority on public-health administration and has written a book which is worthy of a place in the doctor's library.